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Additional confirmatory evidence that estradiol dipropionate is clinically more effective, mg. for mg., than estradiol benzoate¹ has been presented.¹ Eighty-two per cent of a series of patients maintained on a constant dosage level and treatment frequency with Di-Ovocycin, "Ciba" (α -estradiol dipropionate) suffered a recurrence of symptoms when α -estradiol benzoate was substituted in the same dose and at the same treatment frequency. As relief of symptoms is the primary consideration in treating the menopausal patient, Di-Ovocycin^{*} offers most effective and economical means of treatment.

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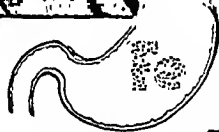
CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

¹ Greene, R. R., J. Clin. Endocrin., 1, 559, July, 1941.

² Freed, S. Chas., Recent Progress in Estrogen Therapy, Meeting of the Illinois State Medical Soc., May 20, 1941, Chicago.

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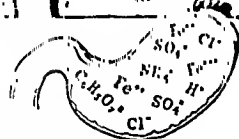
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American Journal of Obstetrics and Gynecology

VOL. 43

JANUARY, 1942

No. 1

Original Communications

NUTRITION STUDY IN PREGNANCY*

DIETARY ANALYSES OF SEVEN-DAY FOOD INTAKE RECORDS OF 514 PREGNANT WOMEN, COMPARISON OF ACTUAL FOOD INTAKES WITH VARIOUSLY STATED REQUIREMENTS, AND RELATIONSHIP OF FOOD INTAKE TO VARIOUS OBSTETRIC FACTORS

PHILIP F. WILLIAMS, M.D., AND FLORENCE G. FRALIN, B.S.

PHILADELPHIA, PA.

(From the Prenatal Clinics of the Presbyterian, Jewish and Philadelphia General Hospitals)

THE dietary inadequacies discovered among the pregnant women in a group of patients followed at the Dental School of the University of Pennsylvania served as a stimulus to study the actual food intake of a large number of pregnant women in Philadelphia. We thought it well to compare the food intake of these women with the variously stated allowances for pregnancy. We wished also to determine any possible relationships between dietary adequacy and various obstetric factors, and complications of pregnancy.

Our interest was further encouraged by the admission of a ward patient with marked clinical pellagra, beriberi, and scurvy at the sixth month of her first pregnancy. These conditions had developed during a period of two months of abstinence from all protein food and vegetables, unfortunately following medical advice. On appropriate vitamin ther-

*This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.

Read, by invitation, at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 3, 1941.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

apy the patient made a quick recovery, was observed in the clinic, and delivered at term a living child, whose weight was slightly over five pounds.

CASE MATERIAL

The study included 514 women. They were selected in a general manner to represent several population, economic, racial, and nationality groups. White women were chosen from the prenatal clinics of the Jewish Hospital, Presbyterian Hospital and the Philadelphia General Hospital. White women from the private practices of three Philadelphia obstetricians, and Italian women from the Starr Centre Prenatal Clinic were also included.

This group represented many sections of the City of Philadelphia and was regarded as appropriate to the problems encountered at the three hospitals. Statistically, however, the sampling was not accurate for the city as a whole. There was too large a percentage of negroes,

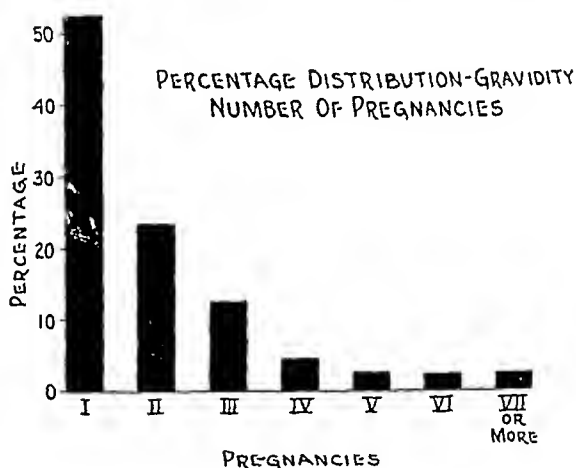


Fig. 1.

too large a proportion of women in the lower age groups, too great a percentage of primigravidas, and, finally, a disproportion between negroes and foreign-born. Probably too many were in the relief class, but at the time this study was begun the proportion, particularly among the negroes, was not as far wrong as it would be today.

ANALYSIS OF THE CASE MATERIAL

There were 382 (74.3 per cent) white women and 132 (25.7) negro women; 436 (84.9 per cent) ward and 78 (15.1 per cent) private patients. By order of pregnancy 271 (52.7 per cent) were primigravidas, 121 (23.5 per cent) secundigravidas, 65 (12.6 per cent) tertigravidas, and 57 (11.2 per cent) other multigravidas, including five who had been pregnant ten or more times (Fig. 1). By stage of gestation, 42 (8.1 per cent) women were in the first trimester; 243 (47.2 per cent) women were in the mid-trimester; 96 (18.7 per cent) women were in the seventh month; 81 (15.9 per cent) women were in the eighth month, and

52 (10.1 per cent) women were in the ninth (Fig. 2). Four hundred and twenty-six (83 per cent) women were American born; 88 (17 per cent) were foreign born; of the latter group 62 (12 per cent of the total) were Italian.

Age groups showed the following divisions: 20 years and under; 138 (26.8 per cent); 21 to 25 years, 152 women (29.6 per cent); 26 to 30 years, 112 women (21.8 per cent); 31 to 35 years; 72 women (14.0 per cent); 36 years and over, 40 women (7.8 per cent) (Fig. 3).

In the 243 parous women, 71 (29 per cent) had had complications in previous pregnancies, while 48 women (19.8 per cent) had had abnormal labors.

The economic status of these women was classified by the income per capita per week, obtained by dividing the total weekly income by the number of persons in the family. Stiebeling and Phipard¹ investigated



Fig. 2.

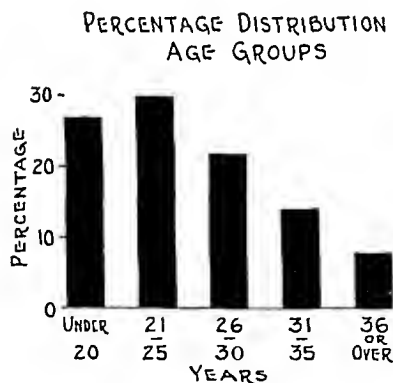


Fig. 3.

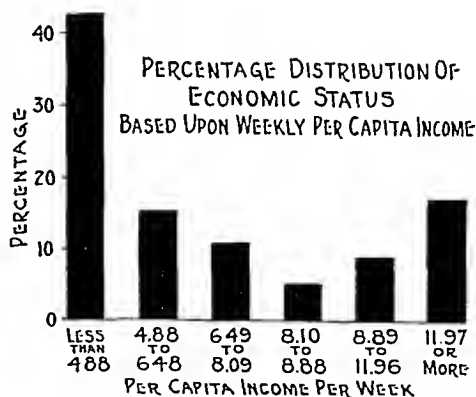


Fig. 4.

the relationships between food expenditures and income for families in various areas, basing income groups on specified sums spent for food. We applied their findings for the North Atlantic area; the groups from lowest to highest, by per capita income per week for white and negro women are shown in Fig. 4. A large proportion of the negro women (82 per cent) were in the lowest income bracket. The economic status of the white patients has been classified in Table I.

Fifty-five women (10.9 per cent), not including those with more than one complication, had toxemias of late pregnancy, characterized by albuminuria, edema, severe headaches, or hypertension. Six (1.2 per cent) women had thyrotoxicosis, mostly of mild degree. Ten (2 per cent) women had ante-partum hemorrhage, placenta previa, or premature separation of the placenta. Pyelocystitis was an ante-partum

TABLE I. ECONOMIC STATUS (WHITE WOMEN)

WEEKLY PER CAPITA INCOME	NUMBER OF CASES	PER CENT OF WHITE WOMEN
Less than \$4.88	111	29.1
\$ 4.89 to \$ 6.48	64	16.8
\$ 6.49 to \$ 8.09	49	12.8
\$ 8.10 to \$ 8.88	25	6.5
\$ 8.89 to \$11.96	44	11.5
\$11.97 and over	89	23.3
	382	100.0

complication in 5 patients (1 per cent), and an equal number had pelvic infections, i.e., reactivation of old salpingitis. Twenty-five other women (5 per cent) had medical complications of various types. Where multiple complications were present, toxemia was always a factor. The histories of the present pregnancies showed that at least 20 per cent of the patients had suffered moderate to marked nausea and vomiting. A similar distribution of other minor symptoms of early toxemia, such as paresthesias and muscle cramps, was recorded.

The present pregnancy, 502 deliveries reported, ended in spontaneous delivery in 366 (72.9 per cent) women. Forceps deliveries, mostly prophylactic low or perineal forceps, terminated 100 (19.9 per cent) of the cases. There were 14 (2.8 per cent) breech deliveries, while cesarean section was resorted to in 19 women (3.8 per cent). Three other operative deliveries were recorded: internal podalic version, supravaginal hysterectomy, and cesarean section, on account of leiomyomas and an operative dilatation of the cervical canal.

Of the 502 deliveries reported, 476 infants (95 per cent), were normal at birth. There were 4 stillbirths. Fourteen babies died during the mother's stay in the hospital. There were 5 pairs of twins, and 2 monsters. One stillbirth was premature and 10 neonatal deaths occurred in premature infants.

The child's weight was not recorded in 20 cases. Twenty-nine (5.8 per cent) of the babies weighed less than 2,500 Gm. Two hundred and seventy-eight (56.3 per cent) showed between 2,500 and 3,499 Gm.; 144 (29.2 per cent), 3,500 to 3,999 Gm.; and 43 (8.3 per cent), 4,000 to 5,400 Gm.

Forty-seven of the women (9.4 per cent) presented sufficient febrile reaction of pelvic origin in the puerperium to be regarded as morbid, according to the standard proposed by the American Committee on Maternal Welfare.² Extragenital infections accounted for puerperal morbidity in an additional 24 (4.8 per cent) women.

In a total of 483 cases in which information was obtainable regarding lactation, 339 mothers (70.2 per cent) breast fed their offspring. Eighty-five (17.6 per cent) of the babies were formula fed during their stay in the hospitals, while 59 (12.2 per cent) were on breast feeding with supplemental formula.

METHODS OF COLLECTING DATA

Methods of collecting dietary information fall into two major categories: (1) Those methods which make use of weighed diets and (2) those which depend upon the estimation of foods actually eaten.

There are, of course, variations in each classification. Weighed diets have many advantages. They are accurate, and they minimize human errors, especially, those due to lack of intelligence in the subjects studied. Measured diets are economical and practical. Many patients do not use scales accurately without supervision, and many are too poor to own or buy them. There are various forms of measured diets. They extend from the very general method of checking food by articles rather than by servings, to the more precise method of measuring foods with ordinary household equipment.

There are several types of food records which employ the measured diet method and which rely upon the memory and integrity of the patient for information. Some are questionnaires, filled out by the worker as she questions the informant regarding her food intake for one or two days. Others are more general and require the patient only to list the number of servings, daily or weekly, of various classes of food. Still others cover a longer period of time and seek meal-to-meal information. These emphasize food actually eaten, rather than food purchased, and give a better picture of the individual's food habits. If the patient records the meal immediately after she has eaten it, the possibilities of omission are lessened. Again, those food records which cover a longer time naturally give more information about food habits.

The food record form which we used was designed to include space for all food eaten during seven days. A nutritionist explained to each woman how to fill in the record properly. She was instructed to write down in detail all foods eaten each day, including regular meals and all food taken between meals. The kinds of each food were to be specified, as well as the amounts in household measures. Milk and other liquids of food value were measured in an eight-ounce measuring cup and recorded in ounces. To illustrate the method, all foods eaten during that day up to the time of the interview were recorded for the patient. Her weight and height, without shoes, were recorded at the first visit. When she returned the food record after seven days, all items were checked carefully with her and necessary corrections or additions were made. The record was then analyzed and the food values were obtained chiefly from "Food Values of Portions Commonly Served."³ By dividing the total value of the food record by seven, we were able to obtain the average daily food intake of each patient.

At the outset of the study in 1939, the vitamin A and the vitamin C values expressed in international units were not available for a great many foods, and those figures which were available presented wide ranges of variation. It was then decided to use the values expressed in Sherman units for vitamins A and C without attempting to convert them into international units. Later, however, when the analyses had been complete, we applied the conversion factors employed by Stiebelling and Phipard in order to make the study more comparable with the

findings of other surveys. Vitamin A values were divided by 2 to obtain international units, and vitamin C values were multiplied by 10. Twenty Sherman units per milligram were allowed when converting these figures to ascorbic acid. The values for vitamin B₁ and D were expressed in international units and for vitamin G (riboflavin) in Sherman units from the beginning of the study.

FOOD FINDINGS

Calories.—The caloric allowance during pregnancy is an unsettled question. On account of the increased metabolic processes of pregnancy one would naturally expect an increased need, but the decreased activities of these women might indicate a lower allowance. Most authorities, however, state that 2,500 calories are the average allowance for pregnant women.^{4, 5} According to the Report of the Technical Com-

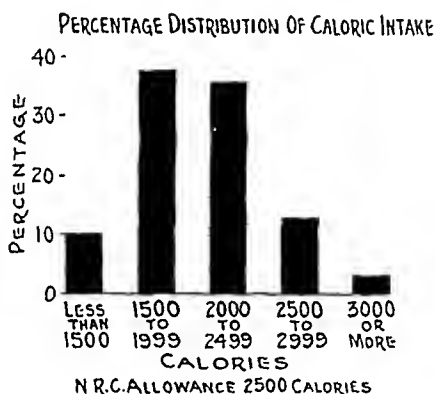


Fig. 5.

mission on Nutrition of the Health Organization of the League of Nations, requirements of pregnant women should be calculated as for normal adult women with an additional allowance for activity.

In our study of 514 food records most of the diets (83.9 per cent) ranged below 2,500 calories (Fig. 5). Two hundred and forty-two (47.1 per cent) had an intake below 2,000 calories; 189 (36.8 per cent), ranged between 2,000 to 2,499. Of the eighty-three women (16.1 per cent) whose diets produced 2,500 calories or above, 67 were between 2,500 and 2,999 calories, 14 between 3,000 and 3,499, and 2 had intakes above 3,500 calories. For the group as a whole the average intake was 2,013 calories; for the white women it was 2,034, and for negroes 1,953.

Protein.—Protein is constantly needed through life for its part in vital processes. Its importance during pregnancy and lactation should be emphasized. The amino acids, derived from metabolism of proteins, are used in growth and tissue repair and after passing through the placenta by simple diffusion, are used by the fetus as available tissue-building material.⁶ A sufficient protein intake in late pregnancy is believed to influence lactation with respect to quality and quantity of milk produced.

Restriction in protein intake in the pregnant woman lowers the nitrogen level, depletes body tissues and leads to nutritional edema. Anemia, poor muscle tone, lowered resistance, and insufficient lactation may also result from protein deficiency.

The protein allowance for the normal human adult has been set at 1 Gm. per kilogram of body weight.^{4, 5} The protein intake recommended for the latter half of pregnancy is 1.5 Gm. per kilogram of body weight.⁴ The National Research Council, in its recommended daily allowances for specific nutrients, states that 85 Gm. should be the daily intake for the average pregnant woman.

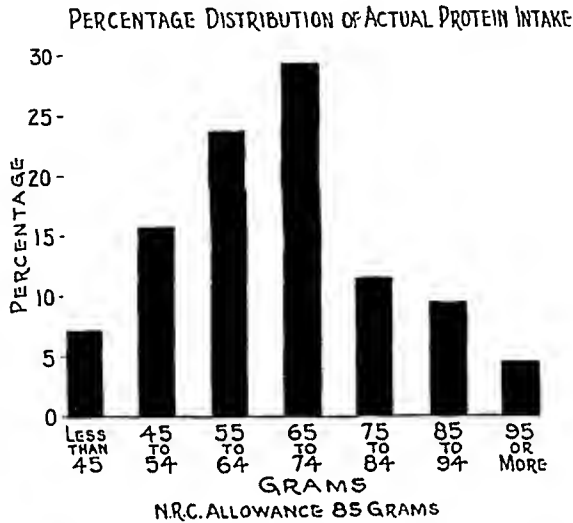


Fig. 6.

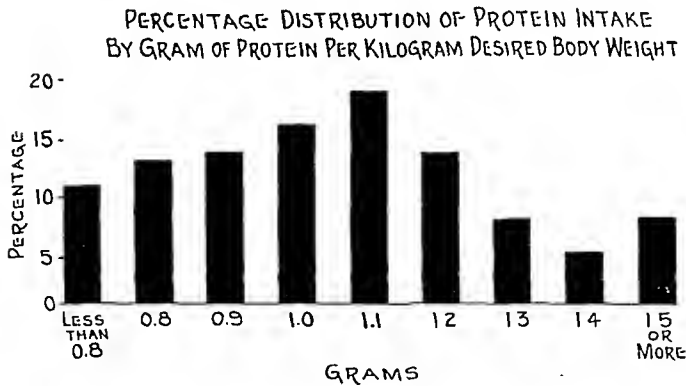


Fig. 7.

Most of the patients (86.9 per cent) in the group studied received less than 85 Gm. of proteins per day, the average was 66 Gm. (Fig. 6). When expressed in terms of desired body weight, 92.7 per cent of the series received less than the estimated requirement of 1.5 Gm. of proteins per kilogram (Fig. 7). The average was 1.1 Gm.*

*Desired body weight was based on height and weight tables for women of the U. S. Public Health Service. To this weight was added an allowance for the stage of pregnancy. A gain of 3 pounds per month was allowed each month after the third. The variations from desired weights are shown in Fig. 8.

Fats and Carbohydrates.—Fats and carbohydrates were regarded merely as sources of energy. If fat should provide 35 per cent of the calories in the human diets, then the diets studied went far above that figure. Ninety-one and four-tenths per cent of the women were consuming diets containing 35 per cent or more calories in the form of fat. The median intake of fat was 41 per cent fat calories. The median carbohydrate intake was 230 Gm.

Calcium and Phosphorus.—The skeletal development of the fetal body and maintenance of the integrity of maternal bony structure are more dependent upon calcium and phosphorus than upon any other inorganic substance. Experiments on domestic and laboratory animals have demonstrated that pregnancy and lactation create extra demands upon the calcium and phosphorus reserves of the mother. The utilization and absorption of calcium and phosphorus are determined by several factors. The most important are calcium-phosphorus ratio, amount of vitamin D available, quantity of fat available, and acid-base balance.^{1, 7}

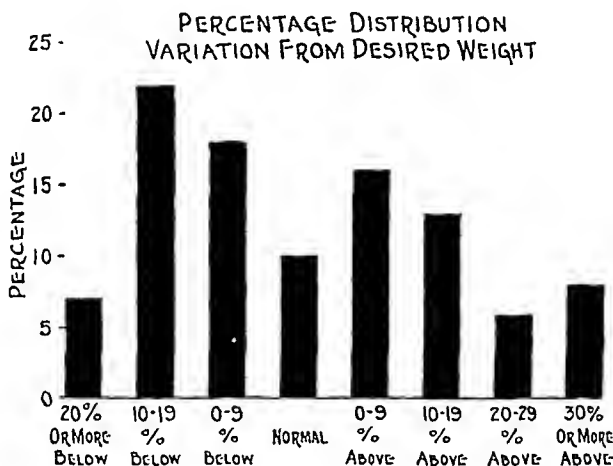


Fig. 8.

The requirement for calcium as recommended by the League of Nations is 0.75 Gm. daily for the normal adult. Pregnancy increases the need to 1.5 Gm. per day.⁵

Where a calcium adequacy exists in the diet, the presence of an adequate amount of phosphorus usually can be assumed. The phosphorus allowances of Stiebelling and Phipard⁴ of 1.32 Gm. per day for all adults of 20 years and over may be accepted as reflecting approximately optimal nutrition of this element.

In our study we found only 15 patients (2.9 per cent) who had calcium intakes of 1.5 Gm. or more per day (Fig. 9). The average calcium intake was 0.7 Gm. The phosphorus intake was 1.3 Gm. or more per day in 369 (71.8 per cent); the average was 1.1 Gm.

Iron.—Iron participates in hemoglobin formation and consequently in the transportation of oxygen. The needs of the pregnant woman are accentuated by the demands of her growing organism, the developing fetus and the necessity for additional storage in the fetus.

The daily adult allowance of iron is believed to range from 12 to 15 mg.⁸ Pregnancy increases the demand, and the allowances vary from

15⁴ to 20 mg.⁹ Only 30 women (5.8 per cent) had an intake of 15 mg. or more (Fig. 10), and the average intake was 10.3 mg.

Vitamin A.—The chief functions of vitamin A in human nutrition in the light of deficiency manifestations are: to maintain the integrity of epithelial tissues; to promote growth, fertility, and reproduction; to promote good tooth structure; to increase resistance to infections; and to regenerate visual purple.

The allowance of vitamin A is dependent upon the weight of the individual. The need in pregnancy is increased on account of accelerated metabolic activities of mother and growing fetus.

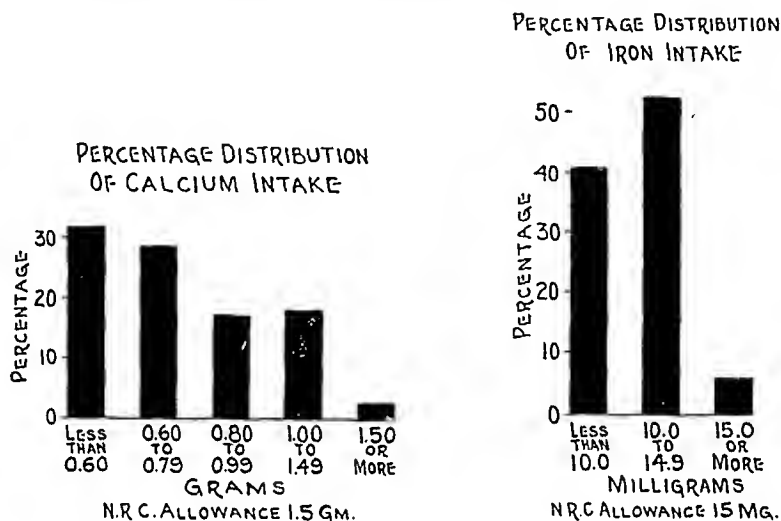


Fig. 9.

Fig. 10.

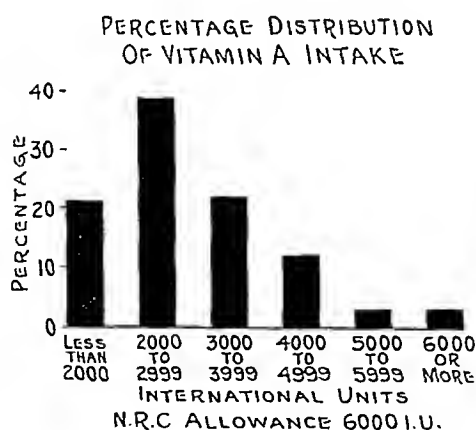


Fig. 11.

The allowance for adults, 20 years and over, has been given as 6,000 international units¹ and 5,000 international units.⁵ The allowance for pregnancy has been stated by the National Research Council as 6,000 international units and by Stiebelling and Phipard¹ as 7,500 international units, while the League of Nations suggests 9,000 international units.

We found that only 18 (3.5 per cent) of the women in this series were receiving this much or more per day. In fact, the intake of more than half of the group was only 2,000 to 4,000 units (Fig. 11). The median was 2,700 units.

Vitamin B₁ (Thiamin).—It is generally accepted that vitamin B₁ plays an important role in the functioning of every cell rather than in the activity of a special organ or tissue system. Its storage is limited and daily replacements must be made. Deficiency in vitamin B₁ may lead to symptoms of varying degree, from the extreme clinical states such as beriberi, to the less well-defined syndrome of fatigue, loss of appetite, and other gastrointestinal symptoms, headache and mild neuritic symptoms.

The requirement of vitamin B₁ bears a distinct relationship both to calorie intake and body weight. Cowgill¹⁰ estimated that the minimum requirement for a normal human adult is approximately 10 international units per 100 calories, or 300 to 350 units per day. This is equivalent to about 1 mg. of thiamin chloride. Increased requirements during pregnancy are conditioned principally by the demands of the fetus and the increased metabolism of the mother.

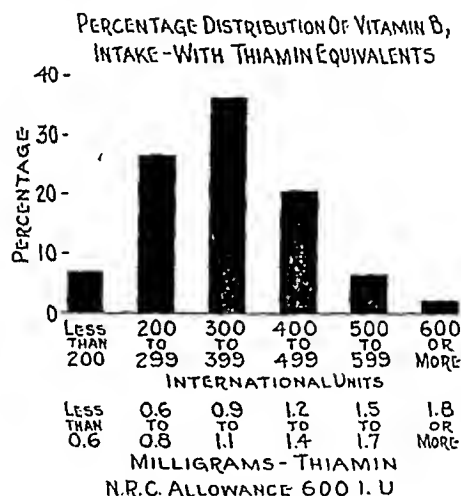


Fig. 12.

The League of Nations⁴ suggested the daily pregnancy requirement of vitamin B₁ at 150 to 250 international units and the National Research Council⁵ recommends 1.8 mg. thiamin chloride (approximately 600 international units vitamin B₁).

Our findings showed that only 9 women (1.8 per cent) received 600 or more international units a day (Fig. 12). More than half of the women had an intake of from 250 to 400 international units daily. The median was 340 units.

Vitamin C (Ascorbic Acid).—The most important function of vitamin C is to control the proper cementing of intercellular material. A deficiency is usually first manifested in tissues, such as teeth, bones, and cartilage, and a severe inadequacy gives rise to scurvy. Its role in combating infections cannot be overlooked. The need for vitamin C is increased during pregnancy on account of the parasitic action of the fetus.

Daily allowances of vitamin C have been recommended as 70 mg. for the moderately active adult woman by the National Research Council.⁵ The allowance for the latter half of pregnancy is 100 mg. of ascorbic acid. The recommendation of the League of Nations⁴ for this vitamin

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is 870 to 1120 international units, or approximately 44 to 56 mg. of ascorbic acid.

In this series adequate vitamin C was furnished in the diets of only 45 patients (8.8 per cent) (Fig. 13). Over one-half received from 30 to 70 mg. of ascorbic acid. The median was 53 mg.

Vitamin G (Riboflavin).—Numerous physiologic roles have been attributed to vitamin G (riboflavin), but the one which has been agreed upon by most authorities is concerned with oxidation processes of the cell. Gross lack of vitamin G in the human being often accompanies other vitamin deficiencies and is characterized chiefly by lesions at the angles of the mouth, at the alae of the nose and on the ears. Because riboflavin acts in part as an enzyme concerned with the metabolism of carbohydrates its allowance has been based on caloric intake.

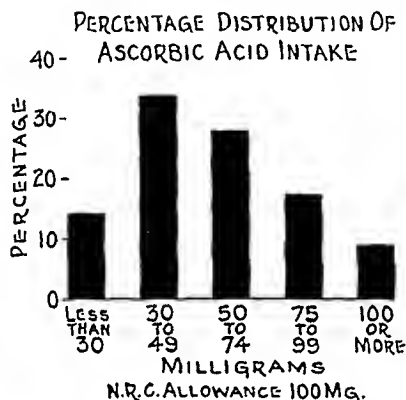


Fig. 13.

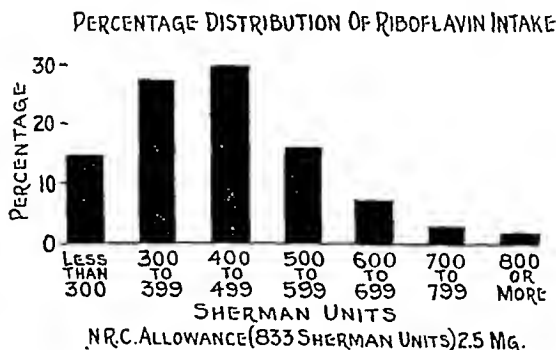


Fig. 14.

The National Research Council⁵ has set the allowance for a moderately active, 70 kilogram man, consuming 3,000 calories daily, at 2.7 mg. For pregnant women, these authorities have defined an allowance of 2.5 mg., presuming that there is an intake of 2,500 calories. Stiebeling and Phipard,¹ although they state no recommendation for pregnancy, suggest 1.8 mg. of riboflavin (600 Sherman units) as the daily allowance for an adult of 20 years or over.

We compared the vitamin G (riboflavin) intake of the group with the Council allowance of 2.5 mg. (approximately 833 Sherman units), and found that only 8 women (1.6 per cent) were receiving that much (Fig. 14). Over one-half of the group were consuming 300 to 500

Sherman units (approximately 0.9 to 1.5 mg. of riboflavin). The average was 420 Sherman units (1.3 mg.).

Vitamin D.—Vitamin D is necessary for the proper formation of bones and teeth by reason of its regulation of calcium and phosphorus utilization. Vitamin D deficiency contributes to the rickets of early childhood. The prematurely born baby requires twice the amount of vitamin D as a full-term baby to prevent the development of rickets.¹¹ From this fact it appears that the need of the woman in late pregnancy is increased.

There is lack of agreement as to the requirement of this vitamin for all age groups, except infancy and very young children, although the League of Nations⁴ recommended 340 international units of vitamin D daily for pregnant and lactating women. To protect a pregnant woman against any possible vitamin D inadequacy, Park¹² suggests an intake of 800 international units daily. The Council recommends 400 to 800 units.

It is not possible to measure the amount of vitamin D received by the women of this group, because the amount of sunshine they received was a variable and unmeasurable quantity. According to the few available vitamin D values for foods, these women received amounts varying from none to 140 international units daily. The frequent use of vitamin D concentrates in all classes of pregnant women insures for a certain proportion a sufficient amount of this factor.

ECONOMIC STATUS AND CORRELATIONS

As previously stated, the economic status of these women was classified by the weekly per capita income, and the totals in each group were given.

Stiebeling and Phipard¹ found that certain trends in consumption of different food factors were apparent when correlated with the economic status. They noted a definite increase in the intake of calories, protein calcium, iron, vitamins A, B, and G, and nicotinic acid among the white families in the North Atlantic Cities.

McCance, Widdowson and Vernon-Roe,¹³ in their study of the diets of pregnant women in England, found that at different economic levels the intake of calories, fat, and carbohydrate was little affected by income. The intake of protein, calcium, phosphorus, iron, and vitamin B rose steadily with increased income.

Our findings, after correlating certain food factors with economic status, are discussed in the following paragraphs (Fig. 15).

Because a large proportion (82 per cent) of the negro women were in the lowest economic group, we did not find it feasible to make any correlations with income.

The average energy intake among the negroes was 1,953 calories. In the white women the average caloric intake was greater in the highest income group than in the lowest income group. The rise, however, was not steady and, therefore, not significant.

The average protein intake in the negro group was 70 Gm. Among the white women of the lowest income group the average protein intake

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was 64 Gm. There was a steady rise to the highest income group whose average was 69 Gm.

The intake of carbohydrate and of fat was not affected by income.

Calcium intake, when correlated with economic status, showed an increase among the white women from lowest to highest income groups from 0.7 to 0.9 Gm. The average intake of calcium among the negroes, 0.6 Gm., was lower than that of the economically lowest white group.

There was a slight rise in iron intake with increasing income. The average for all groups was approximately 10 mg.

In the white group vitamin A intake rose from a median of 2,500 international units in the lowest to 3,000 units in the uppermost economic bracket. The negro group had a median intake of 2,600 units.

ECONOMIC STATUS AND SEVERAL FOOD FACTORS
382 WHITE WOMEN

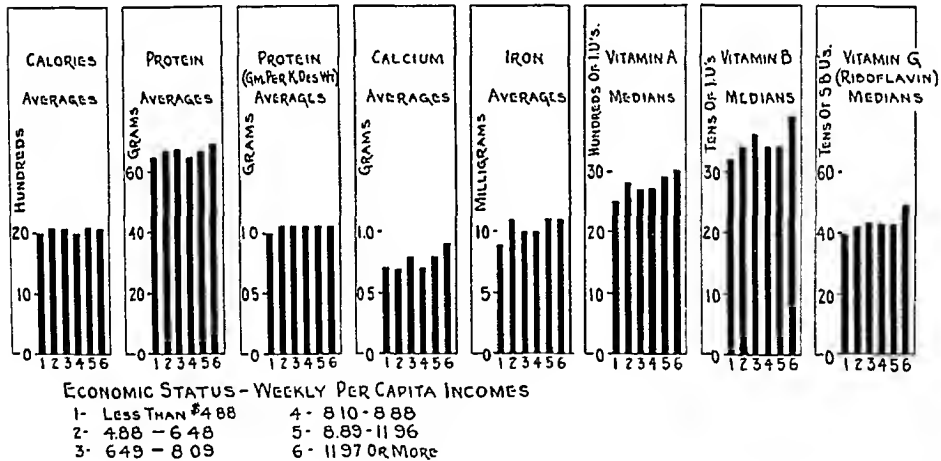


Fig. 15.

The intake of vitamin B₁ in the white women increased from 320 international units in the lowest group to 390 units in the highest. The median for the negro group was 320 units.

The intake of ascorbic acid rose from 46 mg. in the lowest group to 78 mg. in the highest. The median for the negroes was 41 mg.

The intake of vitamin G (riboflavin) definitely followed the increase in income in white women from 390 Sherman units in lowest group to 490 in the highest. The median for the negroes was 400 units.

COMPLICATIONS OF PREGNANCY

To determine the influence of nutritional deficiencies on some complications of pregnancy and childbirth, we have made certain correlations.

In the group with no complications of pregnancy, 392 women, the median intake of protein was 66 Gm.; in the group with various complications, including toxemia, the median intake was 65 Gm.

TOXEMIA

In view of the fact that protein deficiencies have been regarded by some as a possible etiologic factor in toxemias of pregnancy through their influence on protein metabolism, or on serum proteins, we have correlated protein intake with the presence of toxemia. There were 60 cases of toxemia of late pregnancy: 46 were mild pre-eclampsia, 6 were severe pre-eclampsia, and 8 were hypertensive cardiovascular disease. The median protein intake for this group of toxemias was 67 Gm. Since in the normal group we found protein intakes as low as 30 Gm., and since in the toxemia group the most severe cases did not show the lowest protein intake, our findings do not bear out the above-mentioned theory. Comparing the normal and toxemic groups on the basis of grams of protein per kilogram of desired body weight, we found the same lack of positive correlation, and this held true also for vitamins A and B, the other food factors correlated.

There were too few cases of abortion and hemorrhage, pyelitis, and cystitis, and intercurrent infections to warrant definite conclusions.

In cases which presented a history of nausea and vomiting in early months of pregnancy, or who complained of numbness, fatigue and muscle spasm during the latter months of pregnancy, there was an average intake of 400 international units of vitamin B₁, while 84 per cent of this group had an intake below the pregnancy standard of 600 units of vitamin B₁.

PREMATURITY

In the 502 cases for which delivery records were available, 29 children weighing less than 2,500 Gm. each were born singly, and 3 sets of twins had birth weights below this level. Eighteen of the premature births could be explained by obstetric or medical complications, such as syphilis, toxemia, and rheumatic heart disease. One premature twin delivery could be explained by premature separation of the placenta. In the 11 cases in which no explanation could be found for the single premature birth, the average protein intake was 63.6 Gm. In the 2 sets of twins, where no cause other than the multiple pregnancy existed, the maternal intake of protein was 60 and 61 Gm., respectively. If one compares these figures with the average protein intake of the entire group, which was 66 Gm., it is hardly likely, concluding from this small series, that protein deficiency plays a part in the production of premature labor.

We were not able to prove any relationship between prematurity and vitamin A deficiency, since the median intake for the mothers of premature babies was 3,100 international units, slightly higher than the median for the entire series.

STILLBIRTHS

Four of the pregnancies in this series terminated in stillborn fetuses. All could be explained by obstetric complications.

NEONATAL DEATHS

Fourteen neonatal deaths occurred in the series. The weights of the babies ranged from 500 to 3,500 Gm. Ten of the 14 weighed less than

2,500 Gm. Obstetric factors, such as birth injury, toxemia, premature separation of the placenta, monstrosity, myoma, and pelvic infection accounted for 10, heart disease and syphilis for two, while two others were unexplained. In the 2 cases where no medical or obstetric factor could be found to explain the premature delivery and neonatal death, the diets of the mothers were markedly deficient. These two instances, however, do not warrant any conclusion as to a relationship between neonatal death and poor eating habits.

WEIGHT OF INFANTS

No correlation could be obtained between the weight of the infant and dietary intake. We are inclined to agree with Adair¹⁴ who says, "the birth weight does not seem to be materially increased by abundant nutriment nor is the reduction significant except in actual maternal deficiency diets."

MORBIDITY

Seventy-one women were morbid after delivery. An analysis of the diets of these women showed that in protein and vitamin A and C intake they were not markedly different from the remainder of the group.

LACTATION

The storage of nitrogen in the latter part of pregnancy is essential for adequate lactation, according to Coons and Blunt,¹⁵ and a sufficient intake of protein is necessary to insure such storage. We wanted to know whether those women who were able to nurse their babies had a higher protein intake than those who did not. The 339 who nursed their babies, the 85 whose babies were formula fed, and the 59 whose babies had supplementary feedings, all showed practically similar protein intake. There was a slight increase in the protein intake of the mothers whose babies were formula fed, and the data were investigated for possible relationship between lactation and economic status, but no definite conclusions were reached.

NORMAL GROUP

It was felt desirable to evaluate the food intake of those women who experienced an apparently normal reproductive process and to compare it with the whole series. The selection of this group depended upon several factors: normal pregnancy with no major complications, normal, spontaneous delivery, prophylactic low forceps, or manual assistance in a breech, and a normal child weighing from 2,500 to 4,500 Gm., which was breast fed during the hospital stay. Two hundred and fifty women comprised this group. When we compared their dietary adequacy with that of the entire 514 women, we found no variation in the intake of protein, calories, calcium, iron, vitamins A, B₁, C, and G. The mere fact that a group of women on a diet well below the recommended allowances for good nutrition bore normal children after an apparently normal pregnancy and were able to nurse them during a short observation period does not signify that the standards are being set too high. Rather, let us presume that this is another instance of compensation by nature in its effort to produce living offspring. Only a long-range study could determine the ultimate effect of a poor diet upon both mother and child.

DISCUSSION

Our analysis of diets consumed by 514 women in the maternity services of three Philadelphia hospitals shows that errors in food habits, and inadequate diets were the rule (Fig. 16). This could be attributed

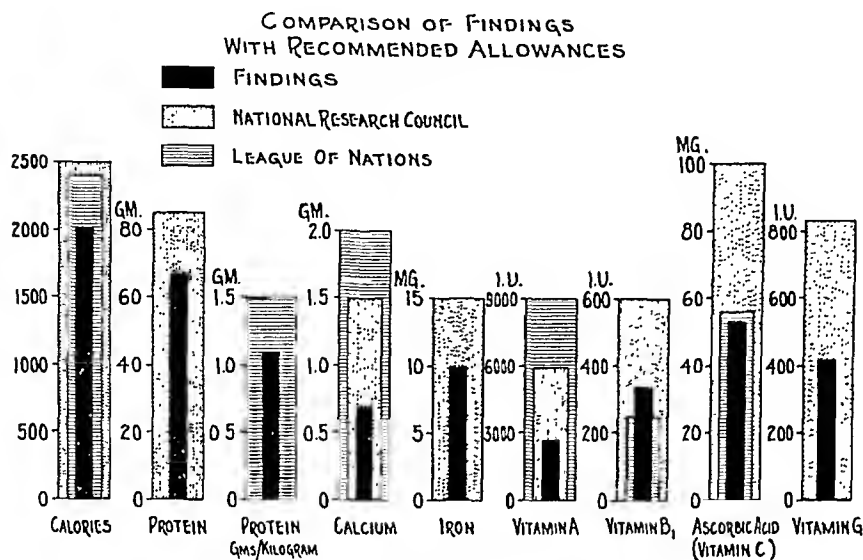


Fig. 16.

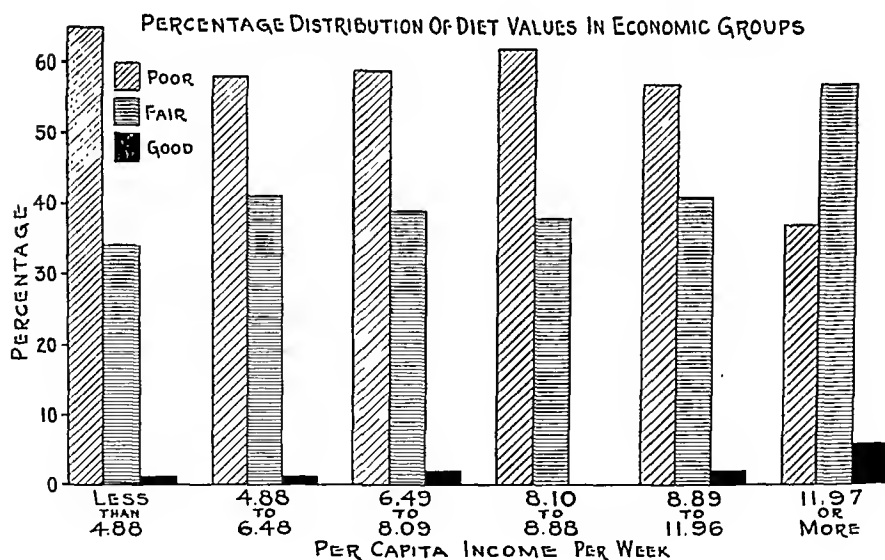


Fig. 17.

in many instances to poor economic circumstances, but often where the income was not low, a lack of knowledge or a disregard of values was responsible for poor diets.

When we applied the yardstick of nutrition of the National Research Council to the assembled data, we found only 10 diets (approximately 2 per cent) met all the requirements and could be termed good (Fig. 17).

A fair diet, between optimal and minimal standards, was found in 209 instances (41 per cent) (Fig. 18). The remainder, 295 (57 per cent) diets, were below the minimal requirements in sufficient number of items that we classed them as poor (Fig. 19). Where one item alone was markedly out of line, calcium deficiency was the most frequently encountered. In establishing a set of minimum standards from the yardstick of nutrition of the Council we followed a procedure previously used by Stiebeling and Phipard.¹ Thus the allowances for vitamins were reduced 50 per cent, and for protein and minerals 33 per cent.

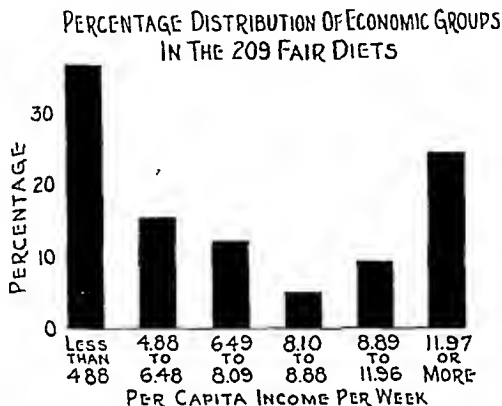


Fig. 18.

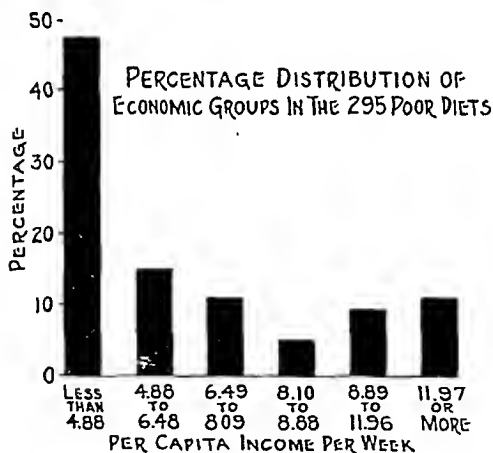


Fig. 19.

Similar instances of bad dietary habits during pregnancy have been noted by other observers.

Burke¹⁶ found only one-fifth of the prenatal cases she studied in Boston met the optimal requirements for calcium, and not one case had an excellent protein intake. Teel¹⁷ found more than one-half of the dietary histories of a small group in Boston deficient in vitamin C. Tompkins¹⁸ observed in Philadelphia an average intake of only 50 Gm. of protein in a group of several hundred prenatal cases. This low protein intake was associated with an excess intake of carbohydrate.

In a study of the diets of mothers of congenitally deformed children in Philadelphia, Murphy and Bowes¹⁹ found marked deficiencies in protective foods. In Maryland, Leamy²⁰ noted that 40 per cent of a group of prenatal cases at one county clinic had an intake of less than 1,000 calories a day, and that only 4 per cent had enough iron in the diet. From another district in Maryland, Whitsitt²¹ states that over 20 per cent of the prenatal cases showed from borderline to frank anemia on a food intake in which the main articles were hog meat, white bread, potatoes, corn syrup, cabbage, and dried beans. Milk, butter, eggs, green vegetables, and fruit were notably absent. Ross and his co-workers²² refer to an equally unbalanced, typically pellagra-producing diet common among pregnant women in some districts of North Carolina. McCahee and others¹³ in England, noted a deficiency in minerals and in total calories in the diets of pregnant women at various economic levels. Ebbs,²³ of Toronto, found that over one-half of a group of 400 pregnant women were consuming diets which he classified as poor.

Such evidence points to a wide prevalence of dietary deficiency among pregnant women. It has recently been announced that the physical examinations of the first million men conducted under Selective Service caused 133,000 to be rejected as unfit for military service from disabilities directly or indirectly connected with nutrition. If a certain percentage of such disabilities in the inductees could be attributed to malnutrition, and we could assume its inception in poor prenatal nutrition, then it behooves us to improve the nutritional status of the next generation.

Education and improvement of economic status are important factors in improving the situation of widespread dietary deficiency in pregnancy. The question of increased income is a problem we do not feel relevant to this paper. We feel assured that through the agency of the Surplus Marketing Administration with its Stamp Plan for the distribution of certain protective foods, and its school luncheon program much good is being accomplished. Particularly, is this true among the twenty million of our population on relief whose average meal, September, 1940, cost five cents, and whose average weekly food expenditure was one dollar.

In the employed wage earner group the entire family and the size of the food budget must be considered carefully in providing an adequate diet for pregnant mothers without depriving the other members. Simple and low cost diets may be arranged which provide adequate intake in practically all nutritive factors. The Children's Bureau by means of poster and pamphlet, "Prenatal Care," have described two such diets. An analysis of these diets shows their content (Table II).

The factor of education is a paramount one in the population as a whole. The problem as it affects us as obstetricians may be summed up in a statement by Burke:¹⁶ "There is no period in life (the prenatal period) where effective and intelligent nutrition teaching would result in greater gains to national health. The reason for this is threefold: first, it would result in improved maternal health and lowered maternal

TABLE II

	CHILDREN'S BUREAU POSTER	"PRENATAL CARE" PAMPHLET	NATIONAL RESEARCH COUNCIL
Protein (Gm.)	92	95	85
Calories	2,614	2,559	2,500
Calcium (Gm.)	1.5	1.6	1.5
Iron (mg.)	16	20	15
Vitamin A (I.U.)	5,785	8,675	6,000
Vitamin B ₁ (I.U.)	500	492	600
Ascorbic acid (mg.)	59	71	100
Vitamin D (I.U.)	84	130	400-800
Riboflavin (mg.)	1.9	2.3	2.5

mortality; second, it would bring about marked improvement in child health and development; third, it would also bring about improved nutrition of the family as a whole."

Research is needed in this problem for more accurate determination of the optimum and minimum requirements of the food factors as well as the conditions which modify their absorption and utilization in pregnancy and lactation. Long term studies with adequate parallel control groups will be necessary to determine the ultimate results in both mother and child. In this respect we realize the limitations of a short run study which we present.

To promote a general improvement of maternal welfare, medical groups must support and continue to support the national nutrition programs now being outlined and instituted. They should lead in individual investigations and more detailed studies in their own areas.

SUMMARY

1. The diets of 514 pregnant women were analyzed with the result that only 10 could be termed good, 209 fair, and 295 poor. They fell much below the standard in all elements when compared with the recommended dietary allowances of the National Research Council.

2. Caloric, carbohydrate, and fat intake were found to be unaffected by income. The intake of vitamin A, vitamin B₁, ascorbic acid, and riboflavin rose with the income. Protein, calcium, and iron showed a slight rise with increased income.

3. This small series did not show any positive relationship between dietary adequacy and the occurrence of certain complications of pregnancy and childbirth. (a) There was no evidence that toxemia occurs in the presence of insufficient protein, vitamin A or vitamin B₁ intake. (b) There were not enough cases of abortion, hemorrhage, pyelitis and cystitis, and intercurrent infections to justify any conclusions. (c) Protein deficiency did not seem responsible for the production of premature labor in a short series of cases. The same may be said for vitamin A. (d) The number of neonatal deaths and stillbirths was too

small to show any positive relationship to dietary inadequacy. (e) The diets of those women who were morbid after delivery did not differ markedly from the remainder of the group with respect to protein, vitamin A, or vitamin C intake. (f) Protein intake apparently had no bearing on the ability of the women to nurse their babies during the hospital stay.

4. Eighty-four per cent of a group who presented a history of nausea and vomiting in early pregnancy had an intake below the pregnancy standard of 600 units of vitamin B₁.

5. Two hundred and fifty women in the series experienced an apparently normal reproductive process. Their food intake showed no variation from that of the entire group of 514.

We are grateful to Mrs. Anna DePlanter Bowes, Dr. Pauline Beery Mack, Dr. R. P. Custer, and Dr. E. D. Burdick for their valued technical assistance, to Dr. F. A. Miller and to Dr. B. Hark for clinical material, and to the social service staffs of the three hospitals where the study was conducted, for their cooperation.

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A CLINICAL EVALUATION OF FETAL ELECTROCARDIOGRAPHY

A STUDY OF 100 CASES BY A NEW TECHNIQUE AND AN IMPROVED INSTRUMENT

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THE recording of fetal heart beats by electrocardiography, while devoid of diagnostic significance with regard to intrinsic cardiac lesions in the fetus, is fast becoming a useful procedure in obstetrics. The technique and instruments employed in this study and our uniform success in obtaining clear records of fetal heart action seem to warrant the addition of this test to the obstetric diagnostic armamentarium. The description of a new technique, by which many previous pitfalls and difficulties are avoided, warrants publication. This study of 100 consecutive, full-term pregnancies terminating in natural labor, yields a normal fetal electrocardiographic standard that is of value to the obstetrician. Many of the obstetric abnormalities encountered are briefly mentioned but no statistical use has been made of this material.

Cremer,¹ in 1906, successfully accomplished fetal electrocardiography when the electrocardiograph was new. His accurate records of the fetal heart in utero showed promise of a new diagnostic aid in obstetrics. Cremer's achievement was followed by a long period during which investigators failed to obtain satisfactory fetal electrocardiograms; and not until 1930, when Maekawa and Toyoshima² took advantage of improvements in electrocardiographic instruments, did the subject become really ripe for further study. In the past ten years numerous records of the fetal heart have been published and various techniques have been outlined.

The technical difficulties involved have been of two kinds: namely, the limitations of the electrocardiograph, and the limitations of the subject. The instrument used was formerly cumbersome, and not sufficiently sensitive to record satisfactory fetal curves. In 1925, the first portable machine was manufactured;³ and in 1932, an improved electrocardiograph⁴ combining light weight, increased sensitivity, and accurate performance was introduced by one of us. This instrument has been developed into the commonly used "Cardiette," an amplifier type of instrument, which has found general acceptance. For the special purpose of this study, the makers of the "Cardiette" have furnished us with an unusually sensitive, improved instrument, which, without sacrificing accuracy and portability, is capable of deflections up to 6 cm. per millivolt, approximately six times the standard sensitivity of the old

string galvanometer. Without such increased sensitivity fetal deflections are so small as to be almost imperceptible. With this instrument, the use of a pre-amplifier or any additional amplifying device is unnecessary.

The limitations of the subject have presented a difficult problem to investigators. The fetus, not directly accessible for electrocardiographic study, is enclosed within the maternal body and cannot be isolated from electrical effects produced by the maternal heart, respiratory muscles, skeletal muscles, etc. The use of an electrode applied to the cervix through the vagina, or of a rectal electrode, presents obvious disadvantages, and can scarcely be developed into a useful routine procedure. Employment of the standard limb leads of the mother has several disadvantages. Elaborate precautions must be taken to secure relaxation and minimize muscle tremor. With increased instrumental

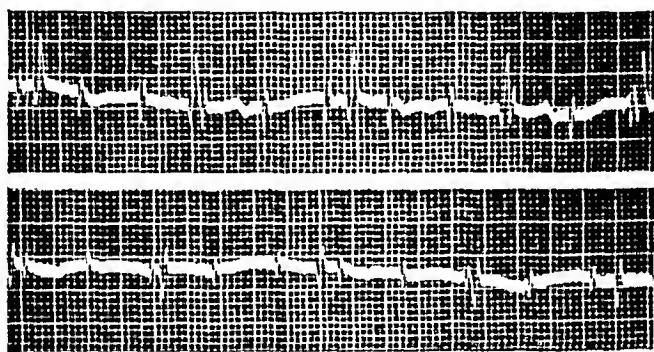


Fig. 1.—Fetal electrocardiograms recorded by the improved method, five days before delivery. The maternal rate is approximately 64 and the fetal rate 155. The upper curve was recorded with electrodes in the second position and the lower curve with the electrodes in the third position. Standardization is 6 cm. per millivolt. Time is in fifths and twenty-fifths of a second.

sensitivity, slight muscle tremors, imperceptible, in the standard electrocardiogram, become evident and impair the record. In addition, the maternal electrocardiogram becomes so enlarged that the smaller fetal deflections are overshadowed and difficult to observe. Most of these difficulties have been overcome by applying electrodes directly to the abdomen of the mother. With the technique to be described, no prolonged period of rest or relaxation is necessary. Tremors due to skeletal muscle are generally absent. The maternal electrocardiogram is so reduced in size that even with maximum instrumental sensitivity, it does not overshadow the fetal deflections. The method presents no complications or difficulties, and offers no possible danger to mother or child. It is eminently suitable as a routine method of fetal electrocardiography, its superiority to other methods being demonstrated by our success in recording fetal curves, not merely during the last forty days before delivery, but as early as the fourth month of gestation. The clarity with which fetal electrocardiograms may be recorded by our method is illustrated in Fig. 1.

TECHNIQUE

This method, developed by Mann,⁵ is carried out as follows: The patient reclines comfortably on an examining table, couch, or bed, either flat or with the head slightly elevated. Smoking, gum chewing, talking, and other nervous stimulation, such as the presence of observers, strong lights, loud sounds, etc., should be eliminated. Corsets or heavy girdles should be removed but light elastic underwear does not interfere and, in fact, may help to hold one electrode in place.

The lower abdomen is exposed and standard electrocardiograph electrodes are applied after rubbing the skin with the usual electrode paste. These electrodes are applied in succession in the following six positions:

The electrodes are covered with a towel or sheet and their position is maintained by the patient's hands, which rest lightly on the sheet. The lower electrode, which is placed below the umbilical level, can often be kept in place by elastic underwear. The right arm wire of the electrocardiograph is connected only to the upper electrode in positions *a*, *b*, *c*, and to the right electrode only, in positions *d*, *e*, *f*. The left arm wire is connected to the other electrode. The instrument is set on Lead I and about thirty maternal deflections are recorded, the first 15 with a sensitivity of 3 cm. per millivolt, and the remaining 15 with a sensitivity of 6 cm. per millivolt. These 30 beats are recorded continuously without stopping the camera, the change in sensitivity being accomplished by simply advancing the sensitivity control to its maximum position after half the record has been taken. Standard millivolt deflections are recorded in the customary manner. In the sixth or last record, it has also been our custom to introduce a signal at five-second intervals, measured with a stop watch, in order to check on the accuracy of the time markings. Occasionally, with rapid maternal heart rates, it may be advisable to record more than 30 beats; and conversely, if the rate is very slow, fewer than 30 beats may be recorded. However, generally, 30 beats will provide a long enough record to enable the fetal deflections to be counted for twenty seconds, so that the fetal rate can be determined with reasonable accuracy. Occasionally, a very nervous or apprehensive patient may be unable to relax and the record may be technically unsatisfactory. In such cases, it has been our custom to proceed exactly as usual with the recording. Upon the patient's next visit, the electrocardiogram is repeated and the patient, having become more familiar with the routine, is invariably more cooperative. An occasional patient may display constant tremor of the large muscles, unusually deep respiration or a persistently rapid heart rate in spite of manifest mental and physical relaxation. In only 2 of the 100 patients did these syndromes frustrate our efforts; in one case there was a muscular tremor with tachycardia, and in the other, a somatic tremor with deep respiration. One of these patients was cardiographed only once and the other only twice, and had greater persistence been employed, final success could have undoubtedly been achieved.

CLINICAL STUDIES

The material for study consisted of successive, unselected patients attending the prenatal clinic. Each patient was cardiographed. As a rule, they did not present themselves until the fifth or sixth month of gestation, but 13 patients were seen before the fifth month. They were

observed in the clinic until parturition; 90 of the birth records were obtained from our own obstetric department and 10 from the other institutions where the labors took place. All premature, abnormal and cesarean section deliveries were excluded. Only full-term patients with

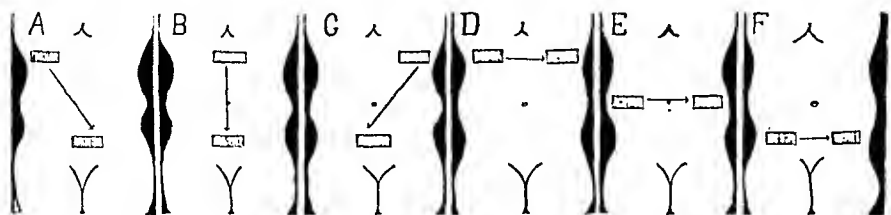


Fig. 2.—The six electrode positions as applied in succession in the new technique. *A*, *B*, and *C* are longitudinal and *D*, *E*, and *F* are transverse. Electrodes are covered with a towel or sheet.

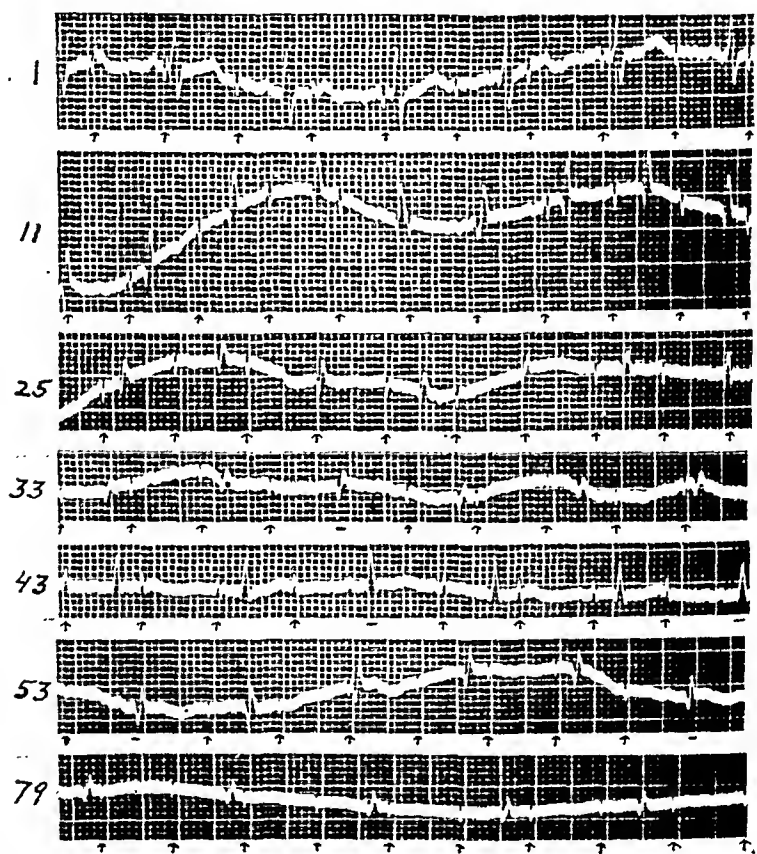


Fig. 3.—Electrocardiograms obtained during the last eighty days of pregnancy. Numerals at left indicate the number of days before delivery when the graph was taken. Maternal deflections are large and slow, widely spaced. Fetal deflections, indicated by arrows, are smaller and more rapid. Standardization is 6 cm. per millivolt.

spontaneous labors, who delivered normal babies, were taken into account. Thus, our electrocardiograms were obtained at accurately determined time intervals before labor. The records and tables, compiled from this unselected group of normal gravidities, therefore, may be offered as an acceptable standard for normal fetal electrocardiography.

Sixty-eight of the women in this series were negroes and 31 were white. (One negro woman was electrocardiographed throughout two consecutive pregnancies.) The ages ranged from sixteen to forty with an average age of about twenty-six years. There were 32 first pregnancies, 29 second, 13 third, 14 fourth, 4 fifth, 5 sixth, and one instance each of seventh, eighth, and tenth pregnancies.

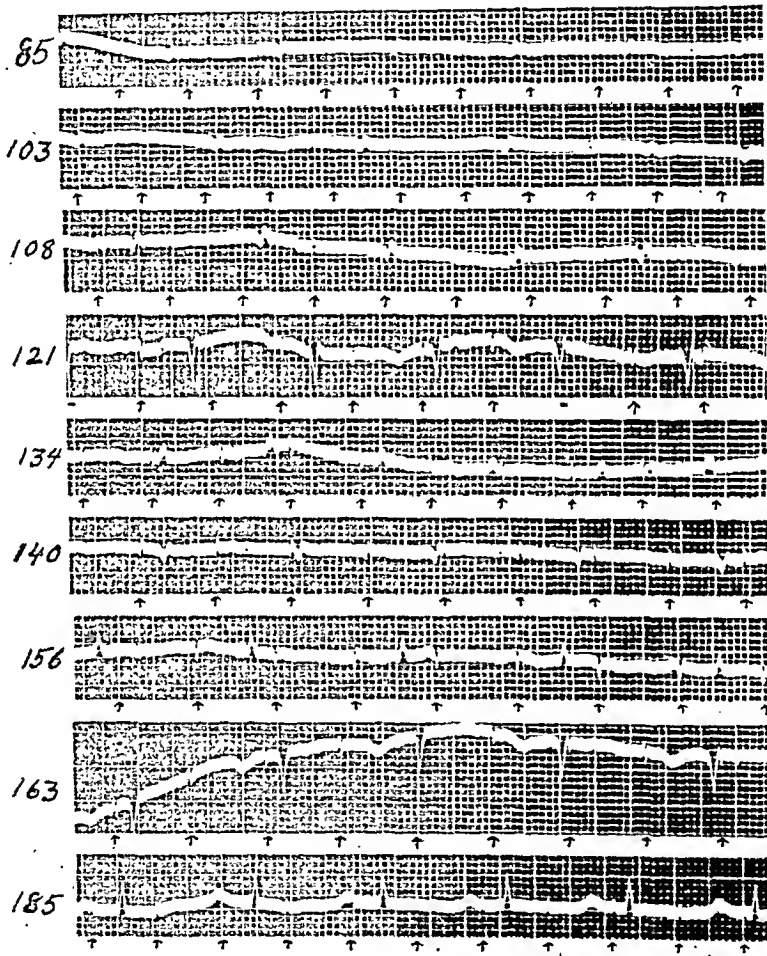


Fig. 4.—Electrocardiograms obtained between the eighty-fifth and one hundred and eighty-fifth day before delivery. The lowermost curve was the earliest obtained, 185 days before delivery. This pregnancy is not admitted to this series, since it was terminated by cesarean section, one day after the inception of labor. Standardization is 6 cm. per millivolt.

Fifty-five male children and 45 female children were delivered. Eighty-two instances of left occipitoanterior position, 14 of right occipitoanterior, and four breech presentations are tabulated from the records. All the mothers and children left the hospital in good health.

Of our 100 patients, only two failed to exhibit a satisfactory fetal curve at some time during pregnancy; one of these was cardiographed only once and the other twice. Both these patients showed marked muscle tremor; in addition one showed unusually deep respiratory excursions and the other had a sinus tachycardia with a rate of about 124. A total of 153 electrocardiograms were taken, the maximum number of records of any patient being 4.

Of these records, 116 (75.8 per cent) showed definite fetal deflections sufficiently clear to permit accurate determination of the fetal heart rate. Thirty-seven (24.2 per cent) did not show satisfactory fetal deflections and were considered negative. Ninety-eight of the 100 patients showed one or more satisfactory fetal curves. Figs. 2 and 3 illustrate typical curves obtained in the last seven lunar months of pregnancy.

The earliest electrocardiograms, four in number, taken in the third lunar month, were all negative. Of 9 records taken in the fourth lunar month, 11 (61 per cent) of 18 records showed definite fetal deflections. In the sixth lunar month, 28 out of 29 (96.5 per cent) curves were satisfactory. In the seventh, the proportion of positive curves decreased somewhat, namely, 14 out of 19 (73.7 per cent); in the eighth month, only 14 out of 26 (53.8 per cent) tests were positive. This sharp drop arouses some speculation as to its cause. In the ninth and tenth lunar months, the high proportion of positive curves reappeared, —26 (96.3 per cent) of 27 graphs and 20 (95.2 per cent) out of 21 graphs, respectively. These findings are presented in Table I.

TABLE I. SHOWING RESULTS OF ELECTROCARDIOGRAPHY FROM THIRD TO TENTH LUNAR MONTHS

LUNAR MONTH	3RD	4TH	5TH	6TH	7TH	8TH	9TH	10TH
Total records taken	4	9	18	29	19	26	27	21
Positive fetal E.C.G.	0	3	11	28	14	14	26	20
Negative fetal E.C.G.	4	6	7	1	5	12	1	1
Per cent positive	0	33	61	96.5	73.7	53.8	96.3	95.2

DISCUSSION

It is interesting that previous investigators in this field report successful fetal records only in the ninth and tenth lunar months. The progressive decline of successful results from 96.5 per cent in the sixth month to 73.7 per cent in the seventh month and to 53.8 per cent in the eighth month is difficult to explain, whereas, in retrospect, the sudden drop from the high percentages in the tenth and ninth months to the low value in the eighth month might lead one to believe that successful electrocardiograms would be increasingly more difficult to obtain in patients during the early months of pregnancy. That this is incorrect is clearly shown by the high percentages observed during the months of the previous trimester. However, tests during the first trimester of pregnancy show a definitely low percentage of successful electrocardiograms (no readings obtained in the third month) in spite of our attempts to obtain these early records with the new instrument and improved technique. We reasonably conclude, therefore, that, under the present new technique, electrocardiography after the fourth lunar month of pregnancy is practicable.

Table I shows that of the 101 records from the fourth month to the eighth month inclusive, 70, or 69.3 per cent, showed positive fetal curves, and during the last two lunar months, 46 out of 48 results were successful, a percentage of 96. During the entire interval from the fourth to

the tenth lunar months, the percentage of success is 77.86 per cent. Thus, the high incidence (96 per cent) of success in the last two lunar months, and, indeed, the fairly high percentage (77.9 per cent) of visible fetal curves obtained during the entire interval, namely, from the fourth to the tenth lunar months, inclusive, would seem to warrant the use of electrocardiography in obstetric work.

The reason why fetal electrocardiograms are not as readily obtainable in certain months, offers interesting material for speculation. Failure to obtain fetal curves during the third lunar month is understandable when one considers the small size of the early fetal heart, and the fact that the fundus at this stage of development is not in contact with the anterior abdominal wall. During the fourth lunar month of gestation, the fetal heart approaches the size of 1 cm. and the surrounding uterine fundus begins to project above the bony pelvis and is at the same time in more constant contact with the anterior abdominal wall. Thus, better contact with the abdominal wall as well as fetal growth, account for the higher percentage of clear fetal heart curves.

It follows also that with the continued increase, month by month, in the size of the fetus and the uterus, a progressively higher degree of successful electrocardiograms should be obtained. We are at a loss, however, to explain the spectacular decrease in the eighth month to a 53.8 per cent incidence. The explanatory conjecture, that during this month a relative or sudden increase in amniotic fluid might insulate the fetus and "short circuit" its electrical output, would seem inadequate, since several electrocardiograms taken in a case of fetal gastroschisis with a 3,000 c.c. hydramnios were indisputably clear and successful. On the contrary, however, in another instance of hydramnios (with twins), the fetal heart rate was unobtainable by electrocardiography during the eighth month of pregnancy. Notwithstanding the former instance, our general experiences would lead us to believe that a fetus close to the abdominal wall presents the optimum condition for successful electrocardiography.

This study permits us to investigate statistically the question of relationship between the fetal heart rate and sex. The average heart rate of the 55 male fetuses recorded in our series was 148.7 beats per minute; and the average rate of the 43 female fetuses was exactly the same. Evidently, an averaging of fetal heart rates gives no indication of the sex of the child. In order to break these figures down for a more detailed analysis, a chart was constructed (Fig. 5). In this chart, male and female, negro and white children are designated by symbolically marked black and white circles, indicating the respective heart rates and time in days before delivery, at which the record was taken. No tendency toward correlation between rate, sex, or color is observed. It seems logical to conclude, therefore, that the fetal heart rate offers no evidence as to the sex of the child.

A study of Fig. 5 does, however, give us some interesting information about the relation of the fetal heart to the duration of pregnancy. The simple average fetal rate in the last six lunar months of pregnancy declines gradually from a maximum of about 165 beats per minute in the fourth month to about 138 in the eighth lunar month, following which there is a rise of a few points in the last two months of pregnancy. This is also indicated in the chart by the broad line, which delineates weighted average rate. It is obvious from a glance at the chart that the spread or individual variation from this average is wide and that conclusions drawn from the average rate should be applied to the individual heart with caution.

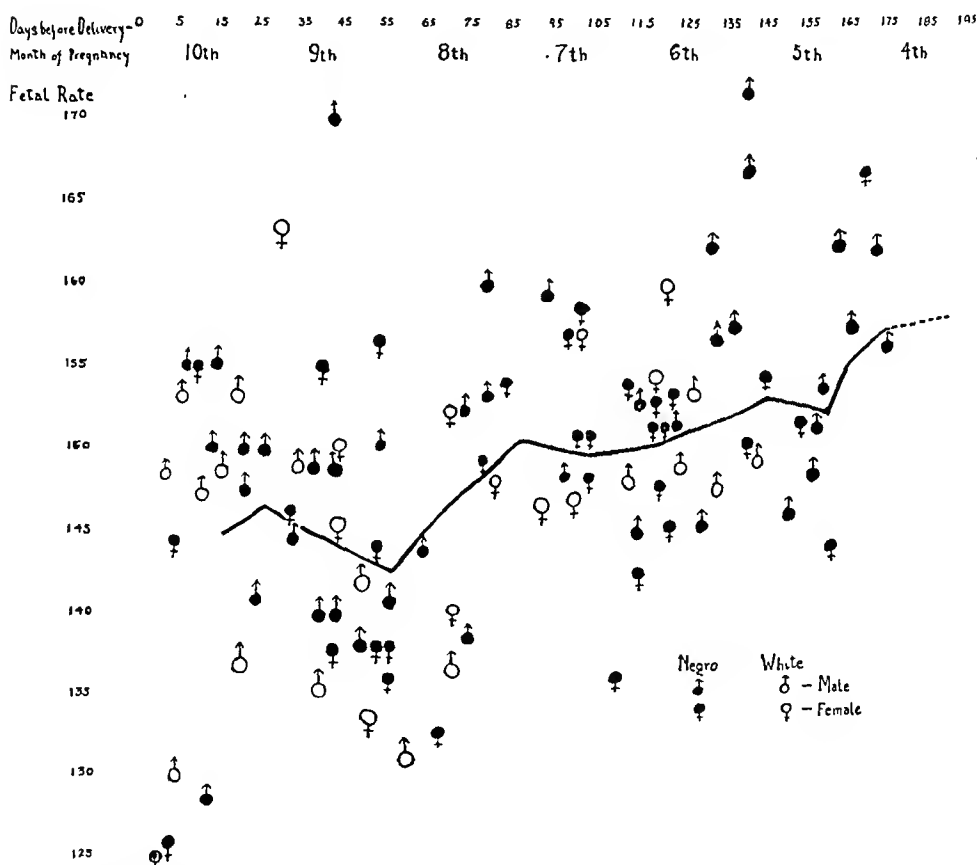


Fig. 5.—Recording of negro and white fetal heart rates in both males and females in the last six and one-half months of pregnancy. The weighted average line indicates a definite and slowly progressive decrease in the fetal heart rate as delivery date is approached. The fetal rate bears no relationship to sex or color.

The question of the relationship between fetal and maternal heart rates may also be subjected to statistical study. The impression that the fetal and maternal rates generally bear some simple ratio or mathematical relation to each other, is not substantiated. This is demonstrated in Fig. 6.

Fig. 6 illustrates graphically the various maternal and fetal rates in our series. Each line represents a single, synchronous determination of a fetal and maternal heart rate. The upper end of the line indicates the fetal heart rate; and the lower end of the line indicates the maternal

rate. The length of the line, therefore, indicates the difference in rate between fetal and maternal hearts. Our chart shows that there is no constant difference in rate between fetal and maternal heart rates, that rapid fetal rates are not indicative of slow maternal rates. Inspection of the chart will show that there is no tendency toward any constant ratio or correlation between fetal and maternal rates.

Abnormal conditions in the mother or fetus were encountered during this investigation. Such cases are not included in the preceding charts and tables but are here reported separately.

Cesarean operation was performed in five instances. These patients all showed positive fetal electrocardiograms. Pseudoeyesis at the menopause simulated pregnancy, as did a large ovarian tumor and fibroid

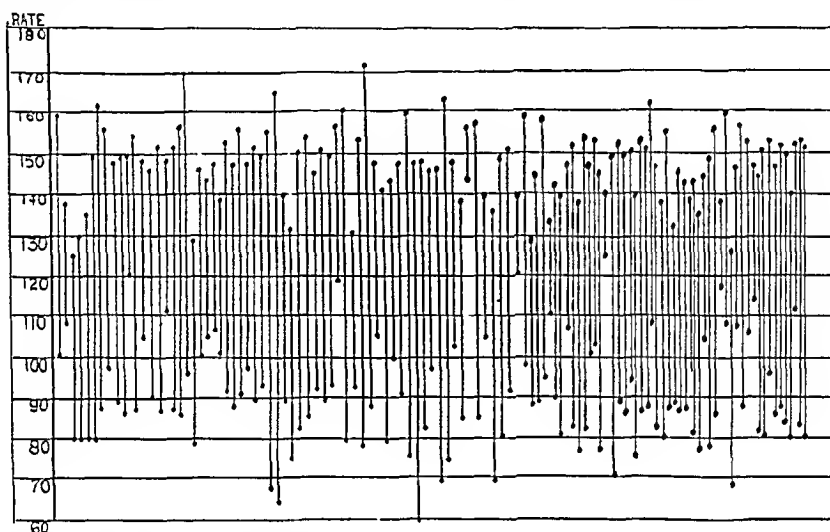


Fig. 6.—Synchronous maternal and fetal heart rates are represented by each line for every reading. The upper end indicates the fetal rate and the lower end, the maternal heart rate. Note complete absence of constant relationship.

uterus, and a missed abortion. These three patients had negative fetal electrocardiograms. In four instances, fetal movements were not felt by the mother, and the fetal heart was inaudible to several physicians; but the fetal electrocardiograms were positive. These four patients all had viable babies.

Two patients had negative fetal electrocardiograms in the fifth month, and aborted macerated gestational products a short while later. One patient, who delivered a viable fetus prematurely at 215 days, had a positive fetal electrocardiogram. Another patient with jaundice, who prematurely delivered a baby weighing 2 pounds, 7 ounces, had a positive fetal electrocardiogram. In another case, two electrocardiograms taken forty-two and six days before labor, showed a rate of 172 and 232 beats per minute, respectively. The patient had an unsuspected gastrochisis fetalis with hydramnios. One patient, whose baby was still-born, at term, had positive fetal electrocardiograms 138 and 110 days before delivery. The time of death may, therefore, be fixed after the one hundred and tenth day before delivery.

One patient, who had had a previous cesarean section before delivery, became sick with vague abdominal symptoms in the seventh month. The electrocardiogram was negative. Ten days later, cesarean delivery of a dead fetus through a ruptured uterus was performed. One patient had twins. Electrocardiograms taken on the day of delivery showed two sets of fetal deflections. The record was a poor one since the mother was having labor pains.

Since the completion of this work and while this paper was being written, 14 of our patients have delivered spontaneously. All fourteen had positive fetal electrocardiograms. None of these, however, are included in this series.

Cardiac arrhythmias in the mothers were rather rare except for the usual sinus and respiratory arrhythmias of varying degree. In two instances, ventricular extrasystoles were recorded, and one patient exhibited transient sinus block, without any evidence of cardiac distress. The fetal heart rates generally showed a moderate degree of sinus arrhythmia, the rate on successive counts varying by as much as 30 beats per minute with an average fluctuation of about 10 beats per minute. In two instances, the record was strongly suggestive of fetal extrasystoles, although the exact nature of the extrasystole could not be determined. In one instance, the fetus exhibited a varying degree of partial block with a rate ranging from 144 per minute to as low as 63 per minute. After birth, this baby exhibited no cardiac abnormality. The anomaly, ectopia cordis, produced peculiar electrocardiograms.

CONCLUSIONS AND SUMMARY

In summarizing the results described in the preceding pages, the following conclusions may be stated:

1. A fair sample, consisting of the first 100 consecutive full-term pregnancies, terminated by normal labors, was studied. In this sample, an almost equal number of parous and nulliparous, white and negro women of all ages, is found. Vertex presentations singularly occurred in all but 4 cases. The number of male and female infants was almost similar.

2. Constancy of method, technique, and personal error was maintained since all tests were performed by one of the authors.

3. A cursory outline of historical data is briefly mentioned along with the technical difficulties previously experienced.

4. A new technique, describing variations in position of electrodes as well as the small convenient portable electrocardiographic instrument, is described. Several complications, inherent physical disturbances, which may alter or obstruct clear recordings, are pointed out. Generally, larger, more obese women yielded inferior electrocardiograms.

5. Only two patients of the entire group failed to exhibit satisfactory fetal curves at some time during pregnancy.

6. Ninety-eight out of 100 patients showed one or more satisfactory curves. The maximum number of records of any single patient was 4.

7. Seventy-five per cent of 153 tests performed on 100 patients showed clear-cut curves. Those which were not clear were considered negative.

8. No positive electrocardiograms were obtainable earlier than the fourth lunar month. In this month, 33 per cent of 9 readings were positive. In the third month no records were successful.

9. The individual monthly percentages of positive results ranged from 53.8 to 96.5 per cent. The average of all monthly percentages, from the fourth to tenth lunar months, inclusive, was 77.86 per cent.

10. In the last two months combined, it is significant that a total of 48 readings yielded 96 per cent positive readings.

11. The fetal heart rate is no index as to the fetal sex, since both sexes averaged 148.7 beats per minute. No correlation between the rate and color of the fetus is found.

12. There was a tendency for a gradual but definite decline in the fetal heart rate to the eighth lunar month; from then on to delivery there was a slight rise. The duration of the pregnancy in any instance cannot be estimated by the rate.

13. Fetal and maternal rates cannot be correlated; a change in one did not necessarily accompany a corresponding alteration in the other.

14. The electrocardiogram furnished a reliable diagnostic test in pseudocyesis of the menopause, suspected pregnancy due to amenorrhea with a large fibroid and huge ovarian cyst, as well as a missed abortion.

15. Electrocardiograms successfully indicated fetal viability in 4 instances in which fetal movements were not felt and in which the fetal heart was inaudible.

16. The presence of multiple pregnancies was accurately diagnosed in one case.

17. A marked rate increase in two cardiograms taken thirty-five days apart within six weeks of labor, proved to be due to an unsuspected anomaly, gastroschisis fetalis with hydramnios.⁶

18. In another teratologic birth, thoracoabdominoschisis with anencephalus, in which the apex of the fetal heart was drawn cephalad in a 180° version by congenital adhesions, the T-waves were inverted. This suggests the possibility of determining a breech presentation.

19. Generally, fetal hearts show sinus arrhythmias and occasionally show extrasystoles and varying degrees of partial block.

20. Intrauterine anomalies usually produce peculiar electrocardiograms in which the rate shows a marked rapidity.

21. Before cesarean section is performed in instances of doubtful viability, an electrocardiogram is indicated.

22. Electrocardiography with the above technique and new instrument was found by us to be a practicable procedure in all pregnancies between the fourth and tenth lunar months.

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1150 FIFTH AVENUE

GLOMERULAR FILTRATION AND RENAL BLOOD FLOW IN THE TOXEMIAS OF PREGNANCY

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SINCE Smith, Goldring and Chasis¹ described the use of "diodrast" at low plasma levels for measuring "effective renal blood flow" this test has been used in several laboratories and has been found to have definite bearing on several clinical entities in which the kidney was suspected but in which previously known renal function tests were found to be normal, namely "essential" hypertension and arteriolar disease.²

The use of inulin as a measurement of glomerular filtration in man³ has also added markedly to the physiologic exploration of renal function and has proved of value in differentiating parenchymatous renal disease from arteriolar disease.⁴

Diodrast in the pregnant woman was first used by Chesley,⁵ who was trying to demonstrate a relationship of "the toxemias" to the hypertensive diseases of the nonpregnant patient.⁶ He was unable to find any evidence of decreased renal blood flow in patients with "toxemias of pregnancy." A similar work was done by Coreoran and Page,⁷ who found significant alteration in blood flow in some of these patients and also found in some of them a noticeably decreased inulin clearance. Welsh, Wellen, and Taylor⁸ have recently shown that in ante-partum patients the inulin clearance is decreased and the diodrast clearance normal or high, and that post partum both clearance values fall.

Because of the high incidence of hypertension following the "toxemia syndrome," we consider it unlikely that the diseases are entirely unrelated; therefore this previous work has been repeated in an effort to classify the clinical stages noted and to show thereby the relationship of "the toxemias" to the hypertensive diseases of the nonpregnant patient.

MATERIALS AND METHODS

Thirty patients were included in this series, and the abnormal patients were classified by the nomenclature recently adopted by the American Committee on Maternal Health.⁹

Eight patients who were within one month of term, had had no previous history of hypertension or toxemia of pregnancy, and who had had no elevation of blood pressure, changes in the retinal vessels or albuminuria during this pregnancy were used as normal controls.

Ten patients who had albuminuria of more than 2 Gm. per day, hypertension, in most cases also edema and a rapid weight gain, but who had no antecedent history of "toxemia of pregnancy" or of hypertension, and whose retinal vessels showed no more than spasm were classified as patients having "severe pre-eclampsia."

Ten patients who had hypertension of moderate to marked degree, some of whom had albuminuria of mild to moderate degree, and who had a previous history of hypertension, eye ground changes, and who usually had had previous "toxemic" pregnancies were classified as having "hypertensive disease."

All clearances were run by the same individual and a standard technique was used:

One thousand cubic centimeters of water were given by mouth the night preceding the test, and 200 c.c. were given at 5:00, 5:30, and 6:00 on the following morning. The bladder was catheterized at 6:00 A.M. with a No. 14 soft rubber catheter and an intravenous drip started at 4 c.c. per minute containing 500 c.c. of 5 per cent glucose, 15 c.c. of 10 per cent inulin* and 15 c.c. of diodrast.† In order to attain an immediate high blood level, a priming solution of 10 c.c. of 10 per cent inulin solution and 1 c.c. of diodrast was given as the drip was started. After a fifteen- to twenty-minute period had elapsed to allow the blood and urine to reach an equilibrium, the bladder was inflated with 50 to 100 c.c. of air three times to expel the remaining urine. From this last expulsion of air to the last expulsion at the end of the clearance, the time was accurately measured to the closest one-half minute. The clearance periods were varied in length in inverse proportion to the urine flow and an effort was made to secure around 80 to 120 c.c. of urine. The usual ante-partum clearance lasted on normal or hypertensive patients from ten to thirty minutes and on toxemic patients from twenty to sixty minutes. Post partum all clearances were run from ten to twenty minutes. Three clearances were run on each patient consecutively in this manner and no attempt was made to keep the urine flow maximum.

Several difficulties have been encountered in doing clearances on women at term. "Pockets" of urine may accumulate in the bladder, which can be found and expressed only with difficulty and which can be missed. It has also been noted in patients with pre-eclampsia and occasionally in the normal that adequate urine flows are impossible to attain. Therefore, we have run clearances at low urine flows on our normal controls and have found that accurate clearances are not obtained for some patients until 1 c.c. a minute and sometimes more has

*Inulin was obtained from the Pfansthiehl Company, Waukegan, Illinois.

†We wish to thank the Winthrop Chemical Company, New York, for part of the diodrast used in this study.

been reached. For this reason, no clearances were figured in the totals where urine flows were less than 1 c.c. per minute, unless they could be checked by comparable values at adequate flows.

Blood samples were taken in the middle of the first and third clearances and values interpolated for the blood values of the second clearance.

Plasma was used in all determinations except urea which was done on whole blood. The plasma and urine were precipitated by the Somogyi technique after incubating each with yeast* for one and one-half hours or more at 37° C. Inulin was determined by the method of Alving, Rubin, and Miller.¹⁰ Diodrast in the earlier experiments was determined by Rolf and White's¹¹ method by hand cooking each tube (we found that the water bath method in our hands did not give constant results). The extraction factor for the blood by this method was considered 86 per cent. The later diodrast determinations were done by Alpert's¹² method. Urea was determined by the manometric method of Van Slyke.¹³

The filtration fraction was determined by $\frac{\text{Inulin clearance}}{\text{Diodrast clearance}}$, the renal blood flow by $\frac{\text{Diodrast clearance}}{1 - \text{Hematocrit}}$. Total serum proteins were done on most patients.

All clearances were rejected which failed to check within 10 per cent of the mean for all three clearances run at the same time. However, in cases in which one of the tests was known to be technically incorrect, this one test was discarded. Where doubt existed as to the validity of the results, clearances were generally checked on another day.

All clearances were calculated on the basis of 1.73 square meters of ideal surface area.

RESULTS

Normal.—The inulin clearance on the normal pregnant patient averaged 116.1 ± 16.9 c.c. per minute (90 to 158 c.c. per minute). There are no inulin clearances available in the literature at this time, but this figure corresponds well with those for normal women reported by Goldring, Chasis, Ranges, and Smith¹⁴ as 118.7 ± 17.5 c.c. per minute. Post partum we found that the normal inulin clearance rose to 139.3 ± 16.1 c.c. per minute (98 to 170 c.c. per minute). (Table I.)

The diodrast clearance in the normal ante-partum patient was found to be 636.5 ± 145.4 c.c. per minute (445 to 860 c.c. per minute), which corresponds to Chesley's⁵ 610 c.c. per minute and that found in normal nonpregnant persons by Goldring¹⁴ of 600.4 ± 87 c.c. per minute. Post partum this clearance was found to be altered insignificantly and the mean was 630.1 ± 90.7 c.c. per minute (438 to 870 c.c. per minute).

The renal blood flow was found to be 950.0 ± 236.7 c.c. per minute (670 to 1,380 c.c. per minute). This seems slightly higher than that

*We wish to thank the Fleischmann Company of New York for supplies of starch-free yeast used in this study.

TABLE I. SUMMARY OF THE DATA ON PATIENTS WHO ARE APPARENTLY CLINICALLY NORMAL†

PATIENT	AGE	PARITY	WEEK	BLOOD PRES-SURE MM.HG	ALBU-MIN	HEMAT-OCRIT %	INULIN CLEARANCE C.C./MIN.	DIODRAST CLEARANCE C.C./MIN.	RENAL BLOOD FLOW C.C./MIN.	URINE FLOW C.C./MIN.	FILTRATION FRACTION	UREA CLEARANCE C.C./MIN.
A-1	31	5-3-2	41	115/78 120/80	Neg. Neg.	36 40	90 136	512 870	890 1,425	0.9 2.4	0.15 0.16	360.0* 648.0
A-2	21	0-0-0	37	110/70 120/80	Neg. Neg.	37 41	96 111	640 660	990 1,120	3.5 1.0	0.16 0.17	— 62.6*
A-3	31	2-1-1	40	120/85 130/85	Neg. Neg.	44 44	110 98	640 610	1,130 1,100	9.4 6.6	0.17 0.16	102.0 64.2
A-4	34	2-1-1	40	130/85 100/70	Neg. Neg.	34 41	123 170	445 640	700 1,000	2.5 2.8	0.27 0.26	137.4 131.4
A-5	40	3-1-2	38	120/80 110/70	Neg. Neg.	37 32	56* 154	500 550	790 810	1.7 7.7	0.11 0.28	70.1* 115.8
A-6	24	2-1-1	38	120/70 110/80	Neg. Neg.	32 35	128 158	820 750	1,200 1,150	2.3 6.7	0.16 0.21	76.6 105.4
A-7	25	1-0-1	32	120/70 110/60	Neg. Neg.	39 45	92 150	484 510	790 930	2.7 3.5	0.19 0.29	116.4 136.1
A-8	32	2-1-1	40	120/80 110/70	Neg. Neg.	34 35	142 120	910 582	1,380 880	6.4 1.7	0.15 0.20	86.6 72.4
Mean Ante partum									950.0	0.176		96.23
									±236.7			±23.2
									±473.4			±46.4
Mean Post partum									979.8	0.234		100.5
									±185.8			±25.7
									±371.6			±51.4

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

†In all tables the first line for each patient represents findings ante partum and the second line findings post partum.

reported by Chesley, but only because approximately half of his patients had a moderate to severe anemia (hematoerit 26 to 31.7 per cent). Post-partum renal blood flow averaged 979.8 ± 185.8 c.c. per minute (680 to 1,425 c.c. per minute).

The filtration fraction was found to average 0.176 (0.15 to 0.29) ante partum and 0.234 (0.16 to 0.36) post partum in these normal patients.

The urea clearances averaged 96.2 ± 23.2 c.c. per minute (76.6 to 158.1 c.c. per minute) ante partum, and 100.5 ± 25.7 c.c. per minute post partum.

Pre-eclampsia.—In patients with the clinical diagnosis of pre-eclampsia, the inulin clearance ante partum was found to be 84.0 ± 35.3 c.c. per minute, which represents a significant decrease. The range, however, is noted to be quite wide (24 to 160 c.c. per minute) and one-third of these cases had a normal clearance. One was definitely elevated above normal. It is noted that patients with a moderate elevation of blood pressure and severe albuminuria usually have a low urine flow and a low inulin clearance, although not without exception (Table II).

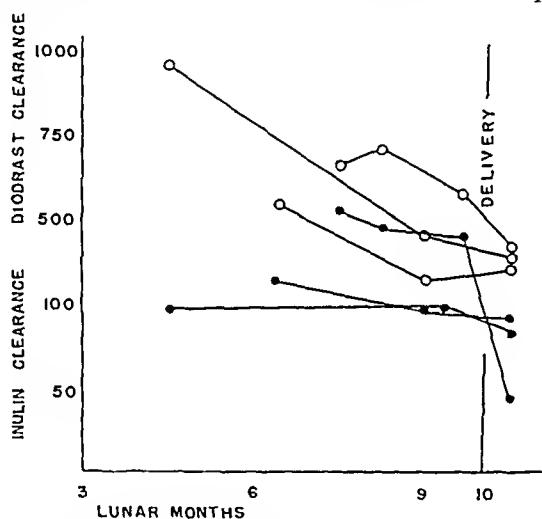


Fig. 1.—Diodrast and inulin clearances in 3 cases of hypertensive disease throughout the period of gestation.

The diodrast clearance in these patients is found to average 680.1 ± 283 c.c. per minute, and to be characteristically normal. A wider variation is noted here than in the normal (178 to 1,440 c.c. per minute) but 50 per cent are easily within normal range.

The filtration fraction is moderately reduced and a few very low values are noted. The urea clearance is definitely depressed (75.1 ± 18 c.c. per minute); the range is probably of no value since a large number of our determinations had to be discarded because the augmentation limit of the urea clearance was below the urine flow.

Post partum we noted a rise in inulin clearance (105.1 ± 38.5 c.c. per minute) such as that in the normal patient, but still not to normal levels. The distribution is wider than normal (35 to 164 c.c. per minute) although the range is normal in more than half of the cases and in them there is a definite tendency toward "high normal" values.

The diodrast clearance post partum shows a definite fall (481.9 ± 179.0 c.c. per minute); here the range is wide (268 to 810 c.c. per

TABLE II. SUMMARY OF THE DATA ON PATIENTS WITH THE CLINICAL DIAGNOSIS OF PRE-ECLAMPSIA

PATIENT	AGE	PARTY	WEEK	BLOOD PRES-SURE	ALBU-MIN	HEM-ATO-CRIT %	INULIN CLEARANCE C.C./MIN.	DIODRASE CLEARANCE C.C./MIN.	RENAL BLOOD FLOW C.C./MIN.	URINE FLOW C.C./MIN.	FILTRATION FRACTION	UREA CLEARANCE C.C./MIN.
B-1	22	1-0-1	38	135/90 140/90	++ +	35 43	110 132 150	460 520 610	700 910 1,020	1.6 2.4 3.5	0.24 0.25 0.24	56.3* 118.6 113.6
B-2	32	1-1-0	40	150/120 140/90	++ Neg.	38 38	80 145 145	327 450 310	530 740 500	3.9 6.1 2.8	0.24 0.31 0.46	61.3 84.9 68.5
B-3	24	1-0-1	39	160/105 140/90	+++ Tr.	36 42	61 138 140	492 520 141	770 900 812	4.9 5.8 12.6	0.12 0.26 0.11	85.3 61.9 51.0
B-4	25	1-1-0	34	160/105 130/90	Tr. ++	37 40	90 138 140	610 770 141	970 920 1,020	1.4 6.7 5.9	0.15 0.25 0.23	49.2* 66.4 72.7
B-5	34	0-0-0	40	160/100 140/100	Tr. Neg.	36 35	160 35 35	610 348 373	1,000 495 535	2.5 4.7 3.8	0.26 0.10 0.09	86.1 57.8 63.5
B-6	27	0-0-0	38	150/100 140/90	+++ +	39 38	140 98 90	690 323 370	1,120 520 600	1.3 5.6 5.2	0.20 0.30 0.24	68.1 66.1 65.0
B-7	22	0-0-0	36	140/90 135/85	+++ +	34 37	90 110 118	942 790 800	1,460 1,250 1,260	0.95 5.9 5.2	0.09 0.14 0.14	84.6 122.1 134.1
B-8	30	1-1-0	39	140/90 130/80	+++ Tr.	41 33	37 164 134	342 372 374	580 600 620	1.0 5.7 6.2	0.11 0.27 0.19	45.7* 110.8 110.4
B-9	22	0-0-0	38	150/100 135/85	+++ +	36 38	45 113 129	292 372 374	455 600 620	1.2 5.9 6.4	0.15 0.30 0.34	33.6* 93.2 110.1
B-10	40	3-0-3	40	140/100 140/100	+++ +	34 40	24 74 64	187 322 346	285 536 550	0.6 0.4 0.7	0.13 0.23 0.19	41.3* 57.0* 53.8*
Mean Anto partum												
							84.0	680.1	905.0		0.167	75.11
							±35.3 ±70.6	±283.2 ±566.4	±425.5 ±851.0			±18.0 ±36.0
Mean Post partum												
							105.1	481.9	745.7		0.228	89.0
							±38.5 ±77.0	±179.0 ±358.0	±192.6 ±385.2			±25.7 ±51.4

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

TABLE III. SUMMARY OF THE DATA ON PATIENTS WITH THE CLINICAL DIAGNOSIS OF HYPERTENSIVE DISEASE

PA- TIENT	AGE	PAR- ITY	WEEK	BLOOD PRES- SURE MM. HG	ALBU- MIN	HEM- ATO- CRIT %	INULIN CLEARANCE G.C./MIN.	DIODRAST CLEARANCE G.C./MIN.		RENAL BLOOD FLOW G.C./MIN.		URINE FLOW G.C./MIN.		FILTRATION FRACTION	UREA CLEARANCE G.C./MIN.		
								330	280	550	468	1.3	0.9			0.23	0.25
C-1	33	2-0-1	37	140/90 135/90	Tr. Neg.	40 40	76 100	330 290	280 330	550 485	468 550	5.3	1.2	0.41	0.30	57.4* 36.2	48.9* 24.3*
C-2	23	1-1-0	41	160/110 140/95	++ Tr.	44 43	12 38	15 25	195 210	350 368	320	0.2	0.2	0.06	0.08	28.2*	
C-3	35	7-1-5	40	135/90	+	40	82		130	135	220	1.4	0.6	0.18		58.6*	83.0*
C-4	34	3-1-1	39	150/90 140/90	Tr. Neg.	37 34	35 76	30 84	200 472	450 460	318 715	6.1	6.4	0.17	0.19	67.9 61.0	55.3
C-5	28	0-0-0	28	170/130 150/100	Neg. Neg.	40 38	144 128	123 119	500 580	590 495	980 854	1.8 9.3	2.5 6.9	0.29 0.22	0.23	101.0 119.8	119.0 114.3
C-6	30	5-1-4	38	150/100 160/110	Neg. +	38 40	86 90	99 88	408 350	383 335	658 580	0.8 6.8	0.5 3.0	0.21 0.25	0.26	31.6* 62.4	27.3* 64.0
C-7	23	1-0-1	39	160/110 130/90	Tr. Neg.	34 32	112 101	115 131	393 344	286 333	435 490	7.4 4.6	3.2 2.5	0.28 0.29	0.40 0.39	52.5* 91.6	35.2* 112.9
C-8	43	7-5-0	40	200/120 150/110	Neg. Neg.	38 40	102 86	86 74	312 430	362 428	500 716	1.8 4.4	1.2 6.2	0.32 0.20	0.23	80.6* 77.1	54.0* 83.4
C-9	38	0-0-0	40	180/110 150/100	++ +	44 33	47 80	53 78	504 410	500 412	900 620	9.3 1.9	6.4 1.2	0.09 0.19	0.10 0.19	57.6 45.7*	57.3 41.5*
C-10	34	2-1-1	38	160/100 150/90	Neg. Neg.	37 40	154 144	143 123	1,090 610	900 606	1,700 1,020	3.0 5.9	6.4 7.0	0.14 0.24	0.16 0.20	111.1 103.5	146.3 106.9
Mean Ante partum															0.228	95.4	
σ																	
2 σ																±31.0 ±62.0	
Mean Post partum															0.234	88.4	
σ																±24.6 ±49.2	
2 σ																	

*All values marked with an asterisk are not included in the calculations of the mean because of low urine flows. All values are reported as maximal clearances.

minute) but half the values are definitely low. A concomitant fall in the renal flow was noted (745.7 ± 192.6 c.e. per minute).

The filtration fraction is normal in average and range.

Urea clearance values tend toward normal but are still below normal post-partum values.

Hypertensive Disease.—The inulin clearance in this group also shows a noticeable reduction (87.0 ± 34.2 c.e. per minute) and the range is quite wide (12 to 154 c.e. per minute); almost one-half of the cases are definitely low. The lowest clearances were obtained in those patients having albuminuria and low urine flows. It is noticeable that two of these patients had a relatively severe type of arteriolar disease (one had hemorrhages in the eye grounds, severe albuminuria and a long history of hypertension and the other 28 years old had a pressure early in pregnancy of 200/130 mm. Hg), yet each had an entirely different clinical course and clearance value.

The diodrast clearances show a definite depression in the ante-partum period (514.8 ± 234.3 c.e. per minute) and the range of values is quite great (130 to 1,090 c.e. per minute) but more than half are definitely low and only one shows a high value (Table III).

The renal blood flow is depressed both ante partum and post partum (693.8 ± 414 and 710.2 ± 193 c.e. per minute).

The filtration fraction is elevated to 0.228 and the range is quite great (0.06-0.41) and most of these values are definitely elevated. When this value is very low there is always also a large decrease in renal blood flow.

The urea clearance is definitely depressed both ante partum and post partum, approximately equivalent to the value noted in patients with pre-eclampsia in the post-partum period (88.4 and 89.0 c.e. per minute) but is not so low as the value found in this group ante partum (95.0 as compared to 75.1 c.e. per minute).

DISCUSSION

It seems obvious from this and previous studies^{7, 8} that the ante-partum inulin clearance is reduced in patients with pre-eclampsia and also in those with hypertensive disease. Renal blood flow in the pre-eclamptic patients is characteristically normal in the ante-partum period, while in the hypertensive group this value is definitely reduced.

Post partum the inulin clearances in both groups tend to return to normal, but the renal blood flow is reduced in both the pre-eclamptic and hypertensive groups, *almost equally* in amount.

The filtration fraction, which has been stressed by Corcoran,⁷ is found to be moderately reduced in our patients with pre-eclampsia and high in the hypertensive group.

The urea clearance is found to be reduced in both groups, more noticeably in the pre-eclamptic series. This is compatible with findings repeatedly reported.^{15, 16}

The value of these studies in the clinical differentiation of patients would seem obvious in some cases. If the patient in the ante-partum period had a low renal blood flow with either a high or low glomerular

filtration, it would be probable that she had a hypertensive disease, and if the renal blood flow were normal, the filtration low, pre-eclampsia would be the likely classification. If both values are normal or high, however, no answer is given to the problem.

Real value could be attached to the test post partum, in addition to careful clinical follow-up, particularly after several months or years. It might then be possible to determine the presence of subclinical or nonhypertensive vascular disease by means of these tests and to be guided by them in allowing the patient to accept responsibility of another pregnancy, assuming that pregnancy causes further damage to patients with vascular disease.

The real interest and value in these tests, however, seems to lie in the study of the physiologic function of the various portions of the kidney associated with this complication of pregnancy.

It is likely that no difference in fundamental pathology exists among those patients who have "toxemia of pregnancy" whether the renal blood flow and filtration rates are high or low, but that functional changes in vascular dynamics are causing these alterations in the mechanism of excretion. This is substantiated by the finding of a wider range of values among "toxemic" patients for diodrast and inulin clearance than that noted among normal patients.

Since the renal blood flow of "toxemic" patients immediately falls post partum to levels below normal and since a clinical diagnosis of one of the syndromes accompanied by hypertension (nephritis, hypertensive disease, etc.) can be made in 40 to 50 per cent of these cases if followed clinically for ten years or more, it would seem that "pre-eclampsia" and "hypertensive disease" are stages in the same process, differing only in that the degree of severity of the disease for these patients as for the nonpregnant hypertensive¹⁷ determines the change in renal blood flow and in filtration fraction.

If we assume that these patients all have the same fundamental disease process, we should be able to show its similarity to that which obtains in the nonpregnant hypertensive as we have been able to find no increased incidence of hypertension in women who have had pregnancies and those who have not been exposed to this hazard.¹⁸

The consistent findings in "hypertensive diseases" in the human being have been: reduced renal blood flow,^{2, 17} an absolute reduction in glomerular filtration,^{17, 19} and an increased filtration fraction.^{2, 17} The basis for these findings has been interpreted as efferent arteriolar constriction, but it seems probable that both afferent and efferent arterioles have increased tone and that the efferent arteriolar constriction is predominant. In these "toxemic" women, we find reduced renal blood flow but also a reduction in filtration fraction. This has been explained by Corcoran⁷ as due to a decreased permeability of the glomerular mem-

brane, but it would seem likely that the glomerulus, as in the nephrotic individual,²⁰ has an increased permeability and should be able to filter faster because of the increased pore-size, so that the picture could better be explained by increased afferent arteriolar tone.

We produced a syndrome in pregnant animals (rabbits and dogs) characterized by albuminuria, hypertension, convulsions, and death with necrosis in the liver, kidney, myocardium, and placentas, by constricting the renal arteries during pregnancy.²¹ We found, however, that the typical syndrome was produced only by minimal constriction of these arteries, and that uremia followed severe constriction.²² Since that time, Schroeder²³ has shown that the renal blood flow in animals with minimal to moderate constriction of these arteries was normal, while it was only after severe constriction that the renal flow was reduced. This work has been confirmed by Page,²⁴ who has shown that the hypertension is dependent on reduction of pulse pressure behind the renal artery clamp.

We have followed three patients with "hypertensive disease" from the earlier parts of gestation through delivery and have observed that pregnancy itself apparently furnishes a factor which tends to keep renal blood flow elevated until the latter part of pregnancy when it drops to lower levels and becomes definitely depressed following delivery.

It would seem likely that the same mechanism for the production of hypertension applies to the woman with "toxemia of pregnancy" as to the nonpregnant hypertensive. The disease is modified by the pregnancy in a quantitative way in that the renal blood flow is maintained despite renal arteriolar constriction of moderate degree and qualitatively in that the afferent arteriolar tone is increased to a greater extent than in the nonpregnant hypertensive, but both differences are merely quantitative modifications of the same fundamental vascular abnormality.

SUMMARY AND CONCLUSIONS

Inulin and diodrast clearances have been done on 10 patients with "pre-eclampsia" and 10 patients with "hypertensive disease."

"Pre-eclampsia" is characterized by a decreased rate of glomerular filtration, a normal renal blood flow and a decrease in the filtration fraction.

Patients with "hypertensive disease" have reduced glomerular filtration and renal blood flow but an elevated filtration fraction.

In both groups of patients post partum the glomerular filtration tends to return toward normal and in both groups the renal blood flow falls well below the normal level.

Evidence is presented in support of the theory that the same fundamental vascular abnormality is responsible for the hypertensive diseases as for the "toxemias of pregnancy" and their sequelae.

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APLASTIC ANEMIA IN PREGNANCY

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INTRODUCTION

THE first case of aplastic anemia, noted in the literature, was described by Ehrlich¹ in 1888, and occurred in a young pregnant woman. Although authenticated instances of aplastic anemia in pregnancy since that time are very few, they present an important problem in obstetric management.

Whether idiopathic aplastic anemia is a true "anemia of pregnancy" or is a coincidental, unrelated phenomenon is still open to question. It is well recognized that any of the blood dyscrasias, as for example acute hemolytic anemia,⁸ sickle cell anemia,⁹ idiopathic purpura hemorrhagica,¹⁰ and leucemia¹¹⁻¹³ may become clinically manifest during the pregnant state. However, in view of the fact that idiopathic aplastic anemia is known to have abated following abortion and in view of other considerations discussed below, it appears that this disease may be a severe, specific complication of the pregnant state.

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There is a dearth of material on this subject in the standard reference works of obstetrics and hematology,¹⁴⁻¹⁷ and in recent reviews of anemia in pregnancy.²⁻⁷ In 1931, Baize¹⁸ collected from the literature 96 cases of idiopathic aplastic anemia, of which 47 occurred in women. Additional reported instances in women since that time bring the total up to 80. The thirteen cases of obstetric interest that are included in this group will be analyzed below.

In many of the case reports of aplastic anemia, the clinical diagnosis lacks biopsy or autopsy confirmation. A case in point is that of Parkes Weber,¹⁹ previously reported as aplastic anemia, found at post mortem to be leucopenic myelosis. Other cases, on close inspection, prove to be instances of pernicious anemia, hematopoietic depression secondary to sepsis, carcinomatosis of the bone marrow, etc. On the other hand, known etiologic agents such as arsenic, benzol intoxication, or irradiation with roentgen rays must be rigidly excluded before a given case may be considered as truly "idiopathic."

Our interest in this subject was stimulated by the occurrence of a case of aplastic anemia in a young pregnant woman, with a rapidly fatal issue.

REPORT OF CASE

Clinical History.—The patient was a 27-year-old white woman, a native of New York, and a typist by occupation. She entered The Mount Sinai Hospital on April 19, 1939, on the medical service of Dr. George Baehr, complaining of profuse bleeding from the gums. The family history was irrelevant. The past history revealed diphtheria during childhood, and a tonsillectomy in 1934. In 1937, the patient's first pregnancy was terminated by curettage.

The last menstrual period occurred three months prior to admission. Shortly thereafter the patient experienced intermittent vomiting, which at times contained brown material. Two months before admission she noted the sudden onset of headaches and subconjunctival hemorrhages. Mild gingival bleeding, previously present, became accentuated, with progressive, spontaneous oozing during the six weeks before admission. In the last three weeks the gingival surfaces had been covered with blood clots.

A fortnight before coming to The Mount Sinai Hospital the patient vomited brownish material and fainted. A blood count at that time revealed a hemoglobin value of 28 per cent (Sahli); erythrocytes 1,800,000 per c.mm.; leucocytes 3,000 per c.mm. of which 90 per cent were lymphocytes; and platelets 30,000 per c.mm. Physical examination was essentially negative except for a few purpuric areas in the skin and profuse intermittent bleeding from the gums. The patient was admitted to another hospital, where she was given five transfusions, parenteral liver extract, and snake venom with no apparent effect. Only a very small amount of material was obtained by a sternal marrow puncture, practically all of the cells being members of the lymphatic series. In a searching history no story of drug ingestion, either as abortifacient or as sedative, or of exposure to noxious substances could be elicited. The patient and her family were emphatic in stating their desire to have the baby.

Physical Examination.—On admission to the Hospital, examination disclosed a well-developed, well-nourished young woman, markedly pallid

and prostrated. The temperature was 101.4° F., pulse 120, and respirations 24. There was a constant ooze of blood from the mouth. No lymphadenopathy was found other than tender submaxillary nodes. A harsh systolic murmur was heard over the entire precordium. The heart and lungs were otherwise not remarkable. The blood pressure was 120 mm. systolic and 60 mm. diastolic. The spleen was not palpable. The uterus was enlarged and soft, rising halfway to the umbilicus; the cervix was very soft. The skin was dry and somewhat scaling, and in places was almost parchment-like.

Laboratory Data.—The following values were obtained on examination of the blood: hemoglobin 42 per cent; erythrocytes 2,230,000 per c.mm.; leucocytes 1,050 per c.mm., of which polymorphonuclear cells were 5 per cent, lymphocytes 94 per cent, and monocytes 1 per cent. and platelets 20,000 per c.mm. Further blood counts are detailed in Table I. The erythrocyte sedimentation time was ten minutes. Both the blood sugar and the urea nitrogen were within normal limits, but the total proteins were low, 4.5 Gm. per 100 c.c. The blood Wassermann reaction was negative; the blood group was 2A. A trace of albumin and occasional leucocytes were found in the urine. The Aschheim-Zondek test for pregnancy was positive. No essential deviations from the normal were seen in the electrocardiogram.

Course and Treatment.—The patient remained alive in the hospital for a period of two and one-half weeks, during which time there was practically a continuous flow of blood from the gums. This could not be controlled by local hemostatic agents, compound bite-blocks applied to the oozing areas as compression splints, and continuous suction under the care of special nurses. During the last week there was also profuse nasal bleeding which required posterior nasal plugs for control. The temperature showed daily elevations between 101° and 102° F. The patient received 16 transfusions of citrated blood. The question of a possible relationship between the pregnant state and the aplastic anemia was raised and the advisability of performing a therapeutic abortion was considered. However, the general condition of the patient never improved sufficiently to make such a procedure feasible.

During the last three days of life, the patient developed progressive edema of the face and vulva. The temperature gradually rose from normal to 106.6° F. On the day before demise, she spontaneously aborted a well-formed male fetus about fourteen weeks of age. Following the abortion there was little vaginal bleeding and apparent cessation of gingival and nasal hemorrhage. The placenta failed to separate and could not be delivered despite instrumentation and the intensive use of oxytocics. Notwithstanding a continuous transfusion, the patient developed generalized purpura and died within twenty-four hours of the abortion, in a delirium of a kind suggestive of hemorrhagic encephalitis.

Pertinent Findings at Necropsy.—The autopsy (No. 11,158), was performed five hours after death. Widespread purpura was present, with extensive petechiae and ecchymoses of the skin, serosal surfaces of the pericardium, pleura, and peritoneum, diaphragm, heart, mucosa of the mouth, stomach, intestines, renal pelves, right ureter, urinary bladder, and uterine cervix. The spleen weighed 200 Gm. and was soft and flabby. The cut surface disclosed a purple red glistening pulp with distinct gray pink follicles and normal trabeculae.

The bone marrow of the ribs, sternum, and vertebrae was yellow-brown in color and dry, except for the lumbar vertebral marrow which

had a faint pink hue. The ribs were extremely thin, and the marrow space appeared as a narrow yellow line.

The right ovary had a freckled blue and red appearance, was semi-firm in consistency, and measured 4 cm. in diameter. On section it was seen to contain a corpus luteum which measured 1.5 cm. in diameter. The left ovary was not remarkable.

The uterine fundus reached a height two-thirds of the way to the umbilicus. The uterus was quite firm and measured about 13 cm. in length, 7 cm. in width, and 5 cm. in depth. The vaginal portion of the cervix was very edematous, thick, ecchymotic, and soft. The vaginal mucosa was studded with purpuric spots. Almost the entire endometrial cavity was occupied by a placenta which was everywhere adherent without any evidence of separation, or even of a well-defined cleavage plane.

Microscopic Examination.—There was no evidence of extramedullary hematopoiesis. A moderate amount of iron was present in the liver, spleen, and bone marrow. A striking hypoplasia of the bone marrow was present. The vertebral marrow appeared slightly less hypoplastic than

TABLE I*

DATE	CITRATE TRANSF. C.C.	HG % SAHLI	R.B.C. MILLIONS/C.M.M.	W.B.C.	STAB.	SEG.	EOS.	MONOS.	LYMPHS.	PLATELETS	RETICS.
4/ 5	1,000	28	1.80	3,000					90	30,000	
4/ 8		46	2.10	1,350	8	8			84	20,000	0.5%
4/ 9	500	42									
4/10	500	45	2.01								
4/11	500	50									
4/15		40	2.18	1,600	6		2	2	90	20,000	0.5%
4/18		37									
4/19	500	30	Admitted to The Mount Sinai Hospital								
4/20	500	42	2.23	1,050	3	2		1	94	20,000	
4/21	500										
4/22	500										
4/24	500	49	2.73	680	6			4	90	20,000	
4/25	500	52	2.38	750	2	4	1	2	91	40,000	0.5%
4/26		47									
4/27	500	40									
4/28	500	35									
4/29		33									
4/30	500	33									
5/ 1		34		950							
5/ 2	500	32		700	2				98		
5/ 3	500	32		800	6				94	30,000	
5/ 4	1,000	31		350							
5/ 5	1,000	32		300	8	2			90		
5/ 6	500			Died							

*The authors are indebted to Dr. Frank Bassen for the privilege of publishing his hematologic findings prior to the admission of the patient to this hospital.

that of the sternum and ribs. All the hematopoietic elements of the marrow were quantitatively reduced, being replaced by fat. The small foci of blood formation that were present were primarily those of erythropoiesis. There was a marked paucity of megalokaryocytes. Adult forms of the granulocytic series were very few.*

*The comparative hematology of the venous blood and sternal marrow in groups of nonpregnant and pregnant women has recently been described by Pitts and Packham.²⁰ The histologic bone marrow findings in a large series of refractory and aplastic anemias are given by Rhoads and Miller.²¹

The uterine musele showed marked hemorrhagic extravasation. There was no evidence of a true placenta accreta.

Examination of the Fetus.—The fetus showed no gross abnormalities. There was no evidence of purpura. The measurements were: crown-rump, 11.5 em.; crown-heel, 16 em. These values coincide with the expected findings in a four-month-old fetus.

Histologically the bone marrow of the mid-humerus, mid-femur, and lumbar vertebrae was active, and without evidence of aplasia. As far as could be determined by comparison with a presumably normal fetus of about the same age, there were no significant changes in the bone marrow, spleen, liver, kidney, or other organs.

CASES OF APLASTIC ANEMIA DURING PREGNANCY

The initial case of aplastic anemia, described by Ehrlich¹ in 1888, was that of a 21-year-old female complaining of uterine bleeding. Curettage revealed fragments of fetal membranes. The erythrocyte count was 213,360 per c.mm. and there was a leucopenia with 80 per cent of the leucocytes being lymphocytes. The patient died within a month without any other bleeding manifestations. At autopsy the bone marrow was found to be yellowish throughout. As Ehrlich states, it was not possible to determine whether the profuse uterine bleeding was caused by an abortion or was the result of a hemorrhagic diathesis.

Because of confusion in terminology, it is difficult to evaluate many of the cases found in the literature, such as those described by Planehard²² in 1887 and by Hanot and Legry²³ in 1889. That profound anemia of an aplastic type can occur with overwhelming infection has long been recognized. Such an instance is the case of Rieea-Barberis,²⁴ in 1908, of aplastic anemia in puerperal sepsis with fatal termination. Similarly, in 1906, Hirschfeld²⁵ reported a case developing after an abortion in a 34-year-old woman, with death in a few weeks. At post-mortem there was found a gangrenous endometritis in addition to an aplastic bone marrow. There were no blood counts, but the patient had known melena for two months. In a second case described by Hirschfeld anemia was discovered in a 28-year-old parturient, with rapid progression and death in nine months. Necropsy disclosed a profound aplasia of the bone marrow.

The first case clinically approximating our own was reported by Massary and Weil²⁶ in 1908. A 21-year-old woman was seen in the fourth month of pregnancy, complaining of epistaxis of three months' duration, purpura of the legs for two months, and gingival bleeding for a few weeks. Physical examination revealed marked pallor, edema of the entire face, and a uterus enlarged to the size of a four months' pregnancy. The erythrocyte count was 776,000 cells per c.mm., and the leucocyte count 5,900 cells per c.mm., of which 58 per cent were polymorphonuclear leucocytes, 35 per cent lymphocytes, and 7 per cent monocytes. Death occurred from heart failure. The fetus and placenta were found to be grossly normal at autopsy. The bone marrow was yellow and poor in formed elements; however, the predominance of megaloblasts over normoblasts, with a decrease in polymorphonuclear cells in relation to myelocytes suggests that this actually may have been a severe case of pernicious anemia.

Jungmann,²⁷ in 1914, described the case of a 29-year-old woman who, at the termination of her third pregnancy, had a severe anemia until three weeks post partum. At the end of her fifth pregnancy she was found to be pale and weak, but not bleeding. The blood hemoglobin was 22 per cent, erythrocytes 1,220,000 per c.mm., and leucocytes 10,000 per c.mm. with 73 per cent segmented neutrophils and 22 per cent lymphocytes. The blood smear showed myelocytes, nucleated red blood cells, macrophages, and a decrease in platelets. At delivery there was no excessive bleeding, and thereafter the patient made a complete recovery. Again, in view of the leucocyte count and the evidence of young forms in the smear of the peripheral blood, the validity of this as an instance of aplastic anemia is open to question. A more suggestive case is that of Larrabee,²⁸ concerning a 30-year-old woman in the third month of her second gestation, who complained of weakness, dyspnea, and vomiting. With the exception of two small superficial ecchymoses, there were no bleeding manifestations. The blood findings were: hemoglobin 20 per cent; erythrocytes 780,000 per c.mm., with 0.4 per cent reticulocytes and no normoblasts; platelets 64,000 per c.mm.; and leucocytes 2,600 per c.mm., of which 48 per cent were polymorphonuclears, 49 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophils. Despite two transfusions the patient died in three weeks, no attempt to terminate pregnancy having been made. No post-mortem examination was performed.

In 1938, Müller²⁹ reported the case of a 28-year-old woman whose second pregnancy terminated in a normal delivery. There was no excessive bleeding, and no vaginal examination had been performed. Following delivery she experienced fever and chills. The uterus was not abnormal, the blood culture was sterile, and there was no clinical or bacteriologic evidence of an infectious process. The blood values were: hemoglobin 25 per cent, erythrocytes 1,400,000 per c.mm., and leucocytes 5,200 per c.mm. with 1.5 per cent polymorphonuclear cells. Subsequently the patient developed petechiae and hemorrhages, her leucocyte count fell to 2,600 per c.mm., of which 84 per cent were lymphocytes, and her platelet count was 110,000 per c.mm. After several transfusions she made a complete recovery. The cause for the disturbed blood picture was not determined.

If we conceive of aplastic anemia as a depression of hematopoiesis in which all of the bone marrow elements are not simultaneously involved to the same degree, the case of Foderl,³⁰ in 1938, comes to mind. Pallor and weakness, but no bleeding tendencies, were noted in the latter part of her third pregnancy by the patient, who was 23 years old. The erythrocyte count was 2,400,000 per c.mm.; the hemoglobin, 35 per cent; the platelets, 250,000 per c.mm.; and the leucocyte count, 4,500 per c.mm., with 45 per cent polymorphonuclears and 48 per cent lymphocytes. Two transfusions were given, delivery was uneventful, and thereupon the maternal blood picture returned to normal. Foderl considered this a normocytic aplastic anemia, resistant to iron and liver, and responding to transfusions.

The case in the literature most closely paralleling ours is that reported by Nieuwenhuis in 1938.³¹ Weakness, dyspnea, and slight epistaxis occurred for the first time during the seventh month of the first pregnancy of an 18½-year-old girl. The uterus was slightly larger than expected from the duration of pregnancy, and the possibility of intrauterine hemorrhage was suspected. Examination of the blood revealed: hemo-

globin 13 per cent; erythrocytes 870,000 per c.mm., with 12 reticulocytes per 1,000 erythrocytes; platelets 12,000 per c.mm.; and leucocytes 1,500 per c.mm., with 81.5 per cent polymorphonuclear leucocytes and 18.5 per cent lymphocytes. Aspiration revealed that the sternal marrow was very poor in cells, with no or at most little signs of activity. No response to therapy was obtained. Accordingly premature labor was induced, and a short-lived grossly normal fetus delivered. Four days later a second marrow aspiration was reported as cellular, and on the sixth postpartum day the hemoglobin level was 42 per cent. Convalescence thereafter was uneventful.

In their analysis of porphyrin excretion in aplastic anemia, Dobriner, Rhoads, and Hummel³² describe six cases, of which one is germane to our subject. A 30-year-old housewife (Case 3) had a chronic aplastic anemia of ten years' duration, discovered when a severe toxemia of pregnancy ended with a miscarriage. At that time her hemoglobin was 27 per cent, but was built up over a period of time to 65 per cent. Following each of two succeeding pregnancies there occurred a severe exacerbation, with improvement after termination of the gravidity. This is the only case of chronic aplastic anemia in this series.

TABLE II

	AGE	STAGE OF PREGNANCY	OBSETERIC MANAGEMENT	OUT-COME	REMARKS
1. Ehrlich, 1888	21	First trimester	Abortion	Death	
2. Planchard, 1887	29	At term	Normal delivery	Death	Diagnosis questionable
3. Hanot and Legry, 1889	25	Second trimester	Miscarriage	Death	Diagnosis questionable
4. Ricca-Barberis, 1908	25	Puerperium	Normal delivery	Death	Sepsis
5. Hirschfeld, 1906	34	First trimester	Abortion	Death	Gangrenous endometritis
6. Hirschfeld, 1906	38	At term	Normal delivery	Death	Died 9 months post partum
7. Massary and Weil, 1908	21	First trimester	Uninterrupted	Death	Death due to heart failure
8. Jungmann, 1914	29	At term	Normal delivery	Recovery	Diagnosis questionable
9. Larrabee, 1925	30	First trimester	Uninterrupted	Death	No post mortem
10. Müller, 1938	28	Post partum	Normal delivery	Recovery	Several transfusions
11. Foderl, 1938	23	Third trimester	Normal delivery	Recovery	Several transfusions
12. Nieuwenhuis, 1938	18	Third trimester	Interrupted	Recovery	Severe case resembling ours
13. Dobriner et al., 1938	30	3 pregnancies	Interrupted	Recovery	Chronic with exacerbations
14. Hurwitt and Field, 1939	27	First trimester	Uninterrupted	Death	Failure of intense therapy

DISCUSSION

From the small number of case reports, it would appear that the occurrence of aplastic anemia during pregnancy is extremely unusual. Nevertheless it is important from the point of view of therapy to determine whether this occurrence is coincidental, or whether in these isolated instances the pregnancy itself may be an etiologic or precipitating

factor. A survey of the published cases of aplastic anemia in females reveals that the average age is in the thirties even though many children are included, whereas in the pregnant group the average age is in the twenties. However it must be recalled that the vast majority of pregnancies occur in the third decade.

Of greater significance is the fate of the aplastic anemia in terms of the course of the pregnancy. In this series of 14 cases, there were 9 deaths and 5 recoveries. The recoveries all took place after pregnancy had been terminated, either normally or by interference.

Among the 9 fatalities, there were 6 patients in whom the uterus had been emptied. Two died with septic complications. In two other cases, those of Planchard and of Hanot and Legry, the diagnosis of aplastic anemia lacked adequate necropsy confirmation. The inadequacy of the hematologic reports in the case of Hirschfeld, the patient dying nine months after delivery, makes analysis of his case difficult. The only clear-cut fatal case, therefore, after the uterus had been emptied of the products of conception, is that of Ehrlich, in which pregnancy had been unsuspected until curettage for uterine bleeding revealed shreds of fetal membranes.

There were only three cases in which the uterus had not been emptied; all three of these patients died. The spontaneous abortion in our case must be regarded as an agonal phenomenon. These three fatalities all occurred during the first trimester of pregnancy, at a time when interruption could most easily have been accomplished.

When we consider the five patients that recovered, the probable significance of the termination of pregnancy appears in an even stronger light. The case of Jungmann, of profound anemia discovered at term with prompt recovery in the puerperium, is not fully established as being one of aplastic anemia. However, the case of Müller, discovered post partum, ran the clinical and hematologic course of an aplastic anemia, with recovery after several transfusions. The remaining three cases were diagnosed while a state of pregnancy still existed. Foderl's patient received two transfusions, went through a normal delivery, and thereafter made an uneventful recovery.

The most convincing evidence that the occurrence of aplastic anemia during pregnancy may be more than mere coincidence is supplied by the case of Nieuwenhuis. The diagnosis of aplastic anemia in the presence of a seven months' gravidity was made clinically and hematologically, and confirmed by bone marrow aspiration. There was no response to any therapy until interruption of the pregnancy, when there was prompt clinical and hematologic improvement. This case differs from ours chiefly in occurring later in pregnancy, and the maintenance of a granulocytosis in the face of leucopenia. The case of Dobriner, Rhoads, and Hummel, with exacerbations during each of three pregnancies and prompt improvement following interruption, strongly suggests a causal relationship. It would be of interest to ascertain the course of subsequent possible pregnancies in these other four women who recovered.

From these considerations it would appear that the indication for the termination of pregnancy in the face of acute aplastic anemia is a most

pressing one. The situation at best is precarious; to procrastinate is to invite a fatal issue. Although interruption of pregnancy had been strongly considered in our case, it was felt that the patient's condition was at all times too poor to warrant interference. However it would appear probable from this review that her only chance for survival would depend on emptying the uterus as soon as she could be strengthened as much as possible. Although apparent clinical improvement may be slight, the blood level may be raised somewhat by transfusions. Certainly the failure of intensive conservative therapy in our case, with almost daily transfusions, as contrasted with the case of Nieuwenhuis, constitutes a most potent argument for advising termination of pregnancy.

In addition to the large groups of cases of anemia in pregnancy attributable to deficiency states or secondary to some manifest condition, sporadic instances are not wanting of profound anemias for which no adequate cause can be found, and which fail to respond to the usual therapy of iron, liver, and transfusions. Many of these recover following termination of the gravidity. An example of this type of case is that of ten Berge,³³ which concerned a 29-year-old woman who was found to have a severe anemia in the eighth month of pregnancy and who promptly recovered following the delivery of a macerated fetus.

Such instances, in addition to the aplastic group, have led many observers to postulate a possible pregnancy toxin as the responsible agent. Certainly such cases as the one above and that of Nieuwenhuis are most highly suggestive that some derangement of pregnancy may be present. The paucity of anatomic abnormalities in the mother and fetus in our case leads one to think of a possible etiology in other than structural terms.

It has been shown by Alice Hamilton in her analysis of benzene as an industrial hazard, that women are not only more susceptible to this substance than men, but that when pregnant they succumb to conditions to which they had previously been tolerant.³⁴ The case described by Dobriner, Rhoads, and Hummel³² is an example in point. Their work on porphyrin excretion would indicate that primary aplastic anemia may result from an intoxication, in contrast to the groups of anemias attributable to deficiency states. Hurst has suggested that an endocrine imbalance may be the basis for idiopathic aplastic anemia.³⁵ An example of this is the occurrence of severe anemia of the aplastic type associated with sclerosis of the thyroid gland which was described by Jaffe.³⁶ The concept of a reciprocal maternal-fetal sensitizing effect, based on an antigen-antibody reaction, is raised by the work of Levine, Katzin, and Burnham on the possible bearing of iso-immunization in pregnancy to the etiology of erythroblastosis fetalis.³⁷ If we are to hypothecate a toxin, a hormonal imbalance, an immunologic change, or some other physiologic disturbance, we must realize that as yet there is no experimental evidence to establish these theories. Nevertheless the conclusion would appear warranted that rarely, during the complex bodily adjustments to a state of pregnancy, a combination of factors may arise predisposing to the development of an aplastic anemia, recovery from which sometimes follows termination of the pregnancy.

SUMMARY AND CONCLUSIONS

1. A case is presented of aplastic anemia occurring during pregnancy, with fatal issue; clinical, laboratory, and pathologic data are given.
2. Eighty cases of primary aplastic anemia in women were collected from the literature; 13 of these were found to be of obstetric significance.
3. Of the total group of 14 cases of aplastic anemia during pregnancy, there were only 5 survivals. In all of these the uterus had been emptied, 2 by normal delivery at term and 2 by interruption during the third trimester. One case developed post partum.
4. A fatality was recorded in each of the 3 cases in which there was no interruption of pregnancy.
5. From the evidence at hand it would appear probable that the occurrence of aplastic anemia during pregnancy may not be coincidental, but that the gravidity may play an etiologic or conditioning role.
6. Interruption of pregnancy should be strongly considered in the presence of aplastic anemia.

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SIMULTANEOUS RADIOLOGIC AND KINETIC RECORDING OF UTERINE AND TUBAL MOTILITY

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THE purpose of this communication is to describe a new technique for the simultaneous radiologic and kinetic study of uterine and tubal motility.

Transuterine insufflation of gas according to the method of Rubin has been employed for the clinical determination of tubal patency and the kymographic pressure tracing has been shown to throw light on certain endocrine levels of the patient. The mechanical factors for the various pressure complexes on these tracings have not been fully explained, and the technique here described may add something in this field.

The anatomic site involved in the complexes, and the nature of the observed muscle phenomena, present, as yet, unsolved fundamental problems. Previous studies have used a variety of approaches to these problems:

1. *In Vitro Experiments With Excised Tubes or Uteri.*—These experiments furnish information about *denervated* organs. In a previous communication,¹ we have shown the important effects of the extrinsic nerves upon insufflation tracings.

2. *Direct Visual or Photographic Studies With and Without a Window.*—This type of experiment is subject to the following possible criticisms:

a. The organs are small and observations are limited to the outer surface of the uterus and tube. The significant changes are in the luminal diameters of these organs. In rabbit insufflation we have seen rippling motions of the tube which are probably due to contractions of the smooth muscle in its mesentery without any obvious effect upon the luminal diameters as observed on the kymograph.

b. The motions are probably slow. In one human patient who was insufflated with the abdomen opened under procaine infiltration of the abdominal wall, we obtained a typical insufflation tracing but could not see any activity of either tube or uterus.

c. Artifacts are constantly being introduced by the motion of adjacent viscera.

3. *Resection of Portions of the Tube.*—Wimpfheimer and Feresten have shown that in rabbits² practically normal tracings could be obtained with most of the tube excised. They attributed the various complexes to the first portion of the extrauterine part of the tube. P. Schneider³ claimed that his x-ray studies suggested that the intrauterine part of the tube was responsible. Obviously, the principle of partial resection furnishes only presumptive, not direct, evidence. In cardiac

physiology, the conduction system maintains the normal cardiac rhythm, and on removing it, a different rhythm is initiated which arises from cardiac musculature itself. Furthermore, the relative importance of the intrauterine and extrauterine portions of the tube is difficult to evaluate in rabbits because of the gradual merging of the two; their surgical division becomes a formidable technical problem.

4. *Radiographic Studies With Contrast Media.*—These have demonstrated peristaltic, antiperistaltic, and segmental contractions in the tubes and also the existence of what has been called a "cornual sphincter" in the intrauterine part of the tube. However, we have found no literature dealing with the correlation between x-ray pictures and simultaneous kinetic studies.

Previous observations on gas insufflation:

Technique of Gas Insufflation.—Gas, usually carbon dioxide, is passed from a tank with a pressure head of 760 mm. Hg through a reducing valve, so that flow is about 30 to 100 c.c. a minute through a cannula placed in the cervix. A recording manometer of the brass aneroid or mercury-float type is incorporated in the apparatus to register the pressure during the insufflation. Usually there is also some device, such as a flow meter, to indicate volume flow of gas.

Type of Pressure Curve Obtained.—In human beings and rabbits similar curves have been obtained. There is a primary pressure peak, A, which is usually the maximum pressure reached before gas enters the abdomen. The pressure then falls to a level, B, the so-called plateau level, which persists throughout the course of several minutes of insufflation. Upon this plateau level are superimposed major C and minor D waves of pressure.

1. The kymographic tracing is essentially a record of perfusion pressure obtained when gas is passed through a hollow system of changing caliber. In studying the behavior of any smooth muscled viscus, the usual stimulus is distention and the response is measured in terms of pressure. In the case of a closed organ, as for instance the urinary bladder (assuming no ureteral reflux), the pressure response to different degrees of volume distention and any resultant rhythmic activity can be recorded easily on any simple manometer. In the case of the uterus and tube, the abdominal ostium permits escape of stimulating media. *This requires a constantly renewed stimulus.*

2. Among the various mechanical factors involved in the study of perfusion pressures are:

a. *Viscosity of Medium:* Gas has low viscosity and the use of fluid as a perfusing medium demands distinct compensations in technique, especially rate of flow. Early experimental attempts to use fluid, frequently resulted in rupture of the thin-walled rabbit uterus because the flow of fluid was not reduced sufficiently to compensate for its high viscosity.

b. *Rate of Flow:* In an inelastic system, the pressure varies directly with the flow. In a previous communication,⁴ we have shown the marked kymographic differences obtained on altering the rate of gas flow. It is true that the organs, in time, tend to compensate to some extent for these changes and preserve a relatively constant pressure.

c. *Total Capacity of System:* For similar flow rates, the pressure varies inversely with the size of the system. Compensations must be

made in animal insufflations for the smaller size of their organs. Furthermore, changes in intra-abdominal pressure directly affect the capacities of these thin-walled, easily compressible organs.

d. *Local Changes in Resistance:* Pressure varies inversely with the square of the radius. In the case of the uterus and tubes, the tube presents the smaller luminal diameter, and small linear changes in its diameter produce greater pressure effects. Contractions of the tube may be one of several observed types, segmental, peristaltic, or anti-peristaltic. In the case of rhythmic segmental contractions, the pressure level rises proportionately to the decrease in luminal diameter and over a period of time depending on the duration of the contraction. The duration of contraction is very important and must be correlated with the rate of flow of the perfusing medium. The observed minor waves

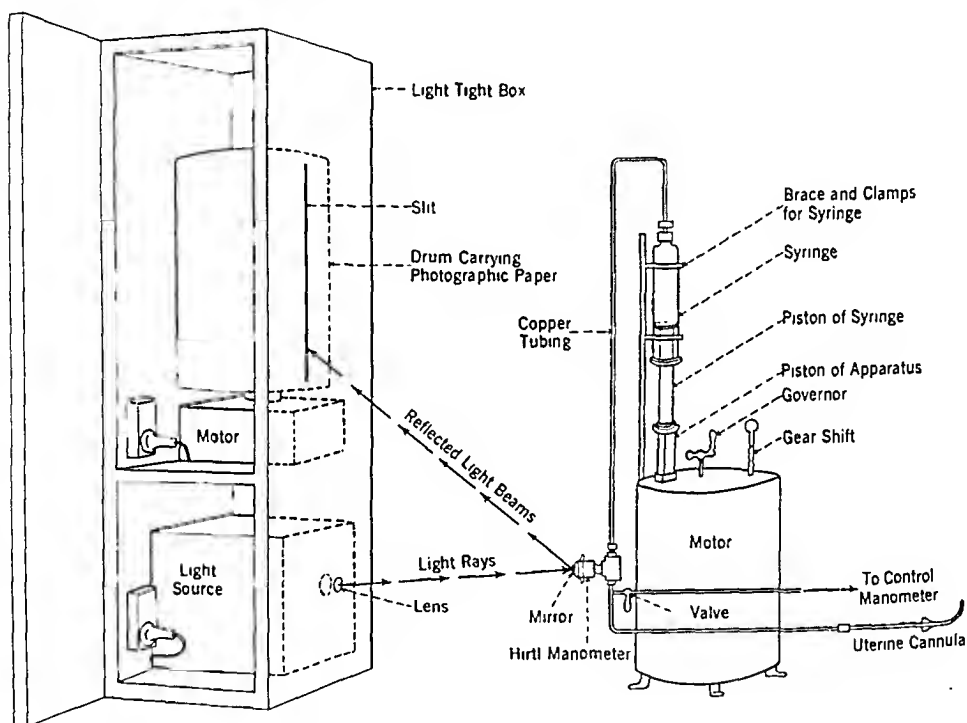


Fig. 1.—Diagram of apparatus used.

of pressure during gas insufflation do not imply that complete closure of the lumen occurs at each rise in pressure. At slow rates of gas flow (30 to 40 c.e. a minute in rabbit investigations), complete closure is probable, for no gas escapes from the fimbriated end of the tube during the rises in pressure. At more rapid rates, gas may escape continuously even though rhythmic pressure oscillations are recorded. The slope of the rise of pressure is an index of the extent of closure. The effect of a peristaltic wave on the recorded pressure is contingent on both the extent of contraction and the speed of the wave. If a propulsive peristaltic wave moving from the uterus to the fimbriated end of the tube carries away a column of medium faster than it is being delivered, the pressure in the system will fall. Slower waves and all waves moving toward the uterus would cause a rise in pressure.

DESCRIPTION OF NEW APPARATUS

1. Perfusing medium: Fluid is used because it is not compressible and its kinetics are easier to interpret than those of gas flowing at a slow rate. Moreover, it can be rendered radiopaque and is a medium of low viscosity. Hippuran (aqueous) was chosen in preference to the more opaque but viscous oily solutions used clinically. Lipiodol would have given better contrasting pictures, but its viscosity produces considerable lag.

2. Constant delivery of the medium is provided by a motor-driven syringe. The rate of flow in this specially devised apparatus can be regulated within a range of 0.1 to 1 c.c. and quick changes in rate are possible by the use of a gear system, like an auto gear shift. The motor driving the syringe is of the synchronous motor type which moves the syringe a unit distance independent of load, until a pressure is generated which exceeds 30 pounds (beyond the working range of these experi-

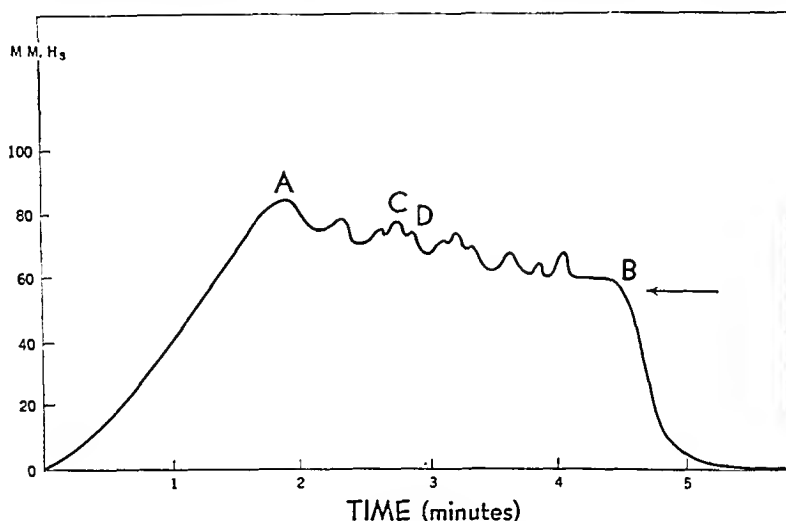


Fig. 2.—Showing typical inflation curve. *A*, Initial rise of pressure. *B*, Pressure plateau. *C*, Major contractions. *D*, Minor contractions.

ments), at which point the motor is arranged to stall. All tubing is of copper. In the clinical gas insufflation apparatus, the flow is not constant enough for this investigative work. In that type of apparatus, the flow is dependent upon the pressure differential between the source of 760 mm. Hg and the working range 0-200 mm. Hg, permitting variations in flow of more than 25 per cent. Furthermore, expansile tubing is used, with its obvious limitations.

3. Continuous pressure records were obtained through a simplified optical manometer incorporated in the system. Inasmuch as the delivery rate is slow and the pressure variations small (0.5 mm. in the minor waves), a sensitive manometer which requires very slight displacements of fluid for recording purposes is of great advantage. The figures comparing the gas-anaeroid system and our fluid-optical drum are

	GAS	FLUID
R—Rate of flow per minute	30 c.c.	0.1 c.c. — 1 c.c.
V—Volume of medium needed to fill manometer to produce a record of 200 mm. Hg	40 c.c.	0.06 c.c.
Ratio of R/V	0.75	1.66 — 16.6

The apparatus is fully sensitive enough to pick up human pulse tracings.

4. Serial x-rays are synchronized to the inflation apparatus, and are taken by means of a continuous strip of radiosensitive paper passed from one lead-lined chamber, crossing under a radiotransparent bakelite window into a lead-lined receiving chamber. The paper is moved along by a hand-driven rubber-covered cylinder and 40 pictures can be taken a minute, allowing 0.3 second intervals for actual exposure time. Appropriate markers on the recording camera indicate the radiograph taken. No such elaborate apparatus was at this time available for our studies in human beings.



Fig. 3.—Normal uterus and tubes; three months post-partum. Medium passing left tube. Isthmic contractions. At this time the pressure was rising and rhythmic waves were registered on the manometer.

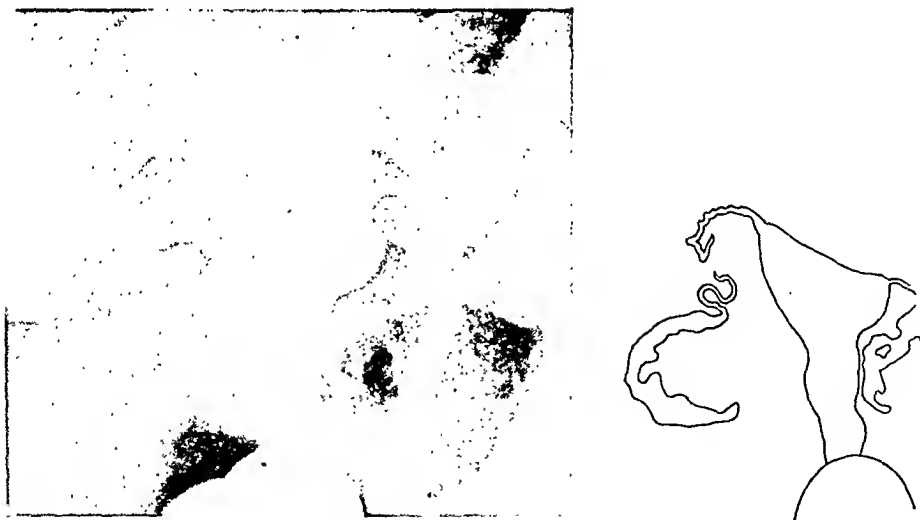


Fig. 4.—Same case. Fluid freely passing both tubes. At this time, pressure waves disappeared.

CLINICAL OBSERVATIONS

1. In two patients who had normal parturition two months previously, no fluid could be driven past the tubes within safe limits of pressure (never exceeding 200 mm.). In each case, however, rhythmic uterine contractions were recorded while the uterus was being distended with fluid. In each case, the x-ray showed the typical funneling at the cornual angle, and the apparent block at the beginning or in the first part of the isthmic portion of the tube.

2. In one patient, who was three months post partum, we obtained a pressure tracing with rhythmic pressure waves of a range of 10 mm. Hg

for a few minutes. An x-ray obtained while the pressure was rising during these waves, revealed the left tube filled with medium, with the exception of the first centimeter of the isthmie portion. This would suggest a tubal contraction in the isthmus. The waves of pressure then disappeared completely, and the plateau level of insufflation pressure fell. An x-ray at this time showed that fluid was pouring through a completely filled right tube, and the left tube was partially filled in its



Fig. 5.—The tube removed for ectopic pregnancy. Fluid in ampulla and in pelvis; none in the isthmie portion during waves of tubal contraction.



Fig. 6.—Normal post-partum uterus. No fluid entering tubes. Visualization of isthmie portion. Terminal regurgitation.

ampullary portion. This would tend to support our previous contention that the usual type of insufflation tracing with small waves of pressure was probably obtained through gas passing through a single tube, rather than both tubes.

3. In two patients with single tubes (the other tubes having been removed for ectopic pregnancies), gas insufflation revealed normal tracings. In these cases, rhythmic waves of pressure were observed

when the fluid passed through the tubes. In both, the rises of pressure were associated with either completely empty tubes, or with medium only in the ampullary portions.

We have performed experiments on numerous rabbits and found the technique feasible. Inasmuch as the Fallopian tubes in the rabbit are extremely narrow, it was necessary to draw them out of the body and place them on a special x-ray table. We are fully aware that the unavoidable displacement of the tubes for the sake of obtaining our visual records introduces a factor which is subject to the criticism of being unphysiologic.

CONCLUSIONS

1. A technique for simultaneous kinetic and radiologic studies on uterine and tubal motility has been described. It should be noted that the need for meticulous control of all factors makes this method, as used at present, a strictly investigative procedure. For instance, the very fact that we are studying a single closed constant perfusion system would invalidate experiments in the event both tubes were patent. Thus, of necessity, we have been restricted in our investigations to cases in which one tube has been removed, i.e., for ectopic pregnancy, and in which the residual tube has been found normal by all available standards.

2. In insufflation of gas or fluid in human beings, the fluctuating waves of pressure are probably isthmic in origin.

We are indebted to Dr. A. Unger, radiologist at Sydenham Hospital, for his invaluable cooperation. We wish to thank the Johnson Research Foundation for their assistance in the acquisition of our apparatus, and Mr. Descoteaux for his technical help.

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Some noteworthy figures are quoted: 79 women, considered in this study, had 1,556 pregnancies, of which 869 terminated in viable births, 212 in spontaneous, and 475 in induced abortions. In terms of percentages, only 55.8 per cent of all conceptions reached viability, 13.6 per cent ended in spontaneous, and 30.5 per cent in induced abortions. Out of 979 women, 636 became pregnant (65 per cent), and 63.8 per cent experienced at least one abortion (spontaneous or induced) which makes 1.7 abortions for each woman. It was found that 90 per cent of these women had married before the age of 30. The largest number of abortions, both spontaneous and induced, occurred during the second month of gestation. The first two pregnancies were most likely to be carried to term. With each subsequent conception the chances of survival for the fetus were sharply reduced. It was also found that the overwhelming number of induced abortions were done by physicians and by means of instruments.

WILLIAM BERMAN.

CHORIONEPITHELIOMA*

A STUDY OF THIRTEEN CASES

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PROBABLY no rare tumor exhibits such markedly malignant characteristics as chorionepithelioma. While the number of reported cases is fairly small in comparison to other malignancies of the female genital tract, their occurrence is common enough and the malignant potentialities so great, as to warrant special attention.

During the years 1925 to 1940 inclusive, 2,042 patients with malignancy of the female genital tract were seen in the Gynecology Clinic of the University of Michigan Hospital. A diagnosis of chorionepithelioma was made in 13 patients, an incidence of 0.63 per cent.

PARITY

The disease occurred twice in primigravidas and eleven times in multiparous patients, coinciding with the majority of reports that chorionepithelioma usually occurs in multiparas. The average parity of the entire group was 2.2 full-term pregnancies. The average gravidity was 3.2 pregnancies. The relation of parity is only of academic interest since multiparas far outnumber primiparas.

AGE

While most other malignant diseases of the female genital tract usually occur during or near the menopause, chorionepitheliomas occur almost entirely during the childbearing period. Our oldest patient was thirty-nine, the youngest nineteen years of age. The average age of the entire group was 28.2 years. Teacher,¹ in his review of 188 cases, claimed that the incidence of chorionepithelioma reaches its peak at the age of 33.

There was one colored patient in our series, the remaining twelve were white.

There exists considerable controversy among the leading authorities regarding the etiology of chorionepithelioma. Most statements propose a possible cause but really offer nothing more than a discussion of the nature of its precursor. Since the cause is still unknown, most of the literature on this point can be summarized by stating that the presence of living chorionic tissue in any location is potentially malignant. Except for the very rare situation wherein chorionepithelioma occurs in a primary tumor of the ovary or in a teratoma, most cases follow moles, abortions, term pregnancies and ectopic pregnancies, and in that order.

Findley² in a report of 500 collected cases of hydatidiform mole found that 157, or 31 per cent, developed chorionepithelioma. Although a sum-

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mary of the world literature by Mathieu³ in 1939 revealed that 10 per cent of moles develop into chorionepithelioma, Mathieu concluded that 50 per cent of chorionepitheliomas are preceded by the passage of moles, the others developing after full-term pregnancies and abortions with emphasis on the latter.

The stress placed on the development of chorionepithelioma following the passage of a mole or an abortion indicates more than the casual interest so frequently displayed in the management of these conditions. The precursor of chorionepithelioma in our series, as compared with that of other authors, is recorded in Table I.

TABLE I. ANTECEDENT CONDITION

	MOLE	ABORTION	FULL TERM	ECTOPIC	UNKNOWN
Schumann ⁴ (15)	8	0	0	0	7
Teacher ¹ (188)	73	59	53	3	0
Mahfouz ⁵ (15)	8	5	1	0	1
Brews ⁶ (24)	8	7	4	0	5
Mathieu ⁸ (28)	15	7	1 associated	0	0
	5 associated				
U. of M. (13)	5	5	3	0	0
Wilson ⁷ (5)	2	2	0	0	1
					(mole 2 yr. before; pregnancy 1 yr. before)

In our series, the average length of time between the occurrence of the predisposing condition and the diagnosis of chorionepithelioma was nineteen months. The longest interval was nine years, following a full-term pregnancy. The shortest interval was ten days, following the delivery of a full-term pregnancy. However, further investigation and analysis of the former's history revealed irregular periods of two years' duration, each menses lasting from five to seven weeks with continuous bleeding for the five months prior to admittance to this hospital. Excepting this case, the longest interval between the appearance of the precursor and the chorionepithelioma was twenty-seven months.

SYMPTOMS

The most characteristic and important symptom of chorionepithelioma is vaginal bleeding. This bleeding may occur shortly after the termination of pregnancy, whether it be a full-term pregnancy, mole, or an abortion, and is due to the corrosive action of the trophoblast on the walls of blood vessels. The latent period may be from several weeks to several months. The bleeding is scant in most cases, gradually increasing in amount as the condition progresses. It is not altogether improbable that bleeding may have existed and then stopped, where the tumor had been totally intramural. The early signs and symptoms are not characteristic and frequently simulate those associated with retained membranes, sepsis and/or involution. The bleeding may be irregular, sudden, severe, or depleting, or the patient may have just a mild amount of serous or serosanguineous discharge.

In Mathieu's⁸ series of 28 cases collected from the entire Pacific Coast region between the years 1931 and 1936, the most frequently noted

symptoms were vaginal bleeding, nausea and vomiting, painful uterine contraction, or no symptoms whatsoever. In our group of cases, vaginal bleeding was the first symptom in 10 patients and chest pain, hemoptysis, and central nervous system symptoms occurred in one of each of the three remaining patients. The cerebral symptoms were headache and blurring of vision. The average duration of symptoms in our group before a diagnosis was made was 6.2 months. The shortest duration of symptoms was three weeks in the patient with cerebral symptoms, the longest duration being twelve months in a patient who had vaginal bleeding following an abortion at three months of gestation. Bleeding following curettement in an incomplete abortion should make the observer suspicious of the possibility of chorionepithelioma. Often, the curette is unable to obtain deep-seated myometrial implants of chorionepithelioma, but even in those where tissue can be obtained, mistakes are frequently made in the microscopic interpretation of the tissue. According to Teacher, it is sometimes very difficult or even impossible to draw a sharp histologic distinction between the villi of simple hydatidiform mole and those of chorionepithelioma. In Schumann's study of 15 cases, he reports one case where the Aschheim-Zondek test was negative and curettings revealed only deciduitis.

Pain as a symptom does not occur until late in the disease. Anemia from acute or chronic hemorrhage may be prominent. Low grade fever, probably on the basis of bacterial invasion of secundines remaining in the uterus, is not uncommon and frank sepsis may be present. The cause of this fever must also be differentiated from secondary pneumonic disease, cerebral processes, from primary incomplete infected abortion, as well as other common causes of fever.

DIAGNOSIS

Prior to the development of the Aschheim-Zondek test in 1928, the diagnosis of chorionepithelioma depended upon the presence of profuse or continuous uterine bleeding, the microscopic appearance of curettings, and the presence or absence of remote metastases. Between the years of 1932 and 1940, the Aschheim-Zondek reaction was utilized in the last 8 cases of chorionepithelioma diagnosed in our clinic. In all 8 patients the Aschheim-Zondek reaction was positive. After admittance to the hospital, the diagnosis was made in all patients in less than ten days after initial admittance. Dilutions of urine were run for the determination of gonadotropic substance on several of the patients and are recorded in Table II.

TABLE II. ASCHHEIM-ZONDEK REACTION

NO. OF CASES	UNDILUTED	1:50	1:100	1:200	1:2000
3	+	0	0	0	0
1	+	+	0	0	0
2	+	+	+	0	0
1	+	+	+	+	0
1	+	+	+	+	+

The value of the Aschheim-Zondek test cannot be too strongly emphasized in dormant cases of chorionepithelioma. It is just as important in the diagnosis of chorionepithelioma as the Kahn test is in the diagnosis

of syphilis. Since mistakes are frequently made in the microscopic diagnosis of the disease, the Aschheim-Zondek test should serve to confirm the microscopic and clinical findings. The biologic test is more accurate than histologic diagnosis on the basis of tissue study. Because of this, considerable skepticism has arisen regarding the true diagnosis of cases so diagnosed before the advent of the test. The biologic test should be utilized in every suspected case in conjunction with clinical examination and the use of other methods which contribute toward making the diagnosis. The concentration of the gonadotropic substance in the urine is not necessarily an important factor in determining the presence or absence of chorionepithelioma, since, in a recent study of women who were seen with normal early pregnancies, positive reactions from these patients' urine, diluted 1:200, were obtained. We feel that any patient who persists in bleeding following a curettage for incomplete abortion or following the evacuation or passage of a mole should be followed by periodic biologic studies. The presence of a positive reaction six weeks after a curettement or passage of a mole should be considered diagnostic of chorionepithelioma. The reaction obtained in the Aschheim-Zondek determination is practically never weak if retained chorion is present. There may, however, be a long latent period of negativity during which time a previously passed molar pregnancy may develop into chorionepithelioma. It is therefore important that frequently repeated tests be carried out in order to make early diagnosis possible. The diagnosis of chorionepithelioma after the appearance of metastases is easy.

Since error in diagnosis may be fatal, more frequent use of the Aschheim-Zondek test is indicated in patients presenting a suspicious abnormality. We prefer the Aschheim-Zondek test, using five mice, rather than the Friedman test with one rabbit, since the chance of detecting early changes is greater. If the mice are killed by the high concentration of gonadotrope or toxic substance in the urine, we favor the repetition of the tests with more dilute specimens.

TREATMENT

Practically all authors agree that once chorionepithelioma has been diagnosed, the proper treatment is immediate hysterectomy. Most observers agree that early diagnosis and adequate early treatment offer the best prospect for cure. Some authors favor subtotal hysterectomy. It is our feeling, however, that if the patient presents even localized malignancy in the uterine wall, the possibility of hematogenous metastases is omnipresent, and for this reason a more radical attack is necessary in order to be certain that all of the neoplasm has been eradicated. We feel that a cure of chorionepithelioma, in the operable case, is based upon total hysterectomy, plus removal of both tubes and ovaries. Preservation of the tubes and ovaries at the time of operation is favored by some, while some gynecologists are influenced in their decision by the presence or absence of ovarian involvement by the primary growth.

If blood loss has been excessive, it should be replaced preoperatively.

TABLE III. METHOD OF TREATMENT

	TOTAL HYSTEREC- TOMY	SUBTOTAL HYSTEREC- TOMY	REMOVAL OF VAG. IMPLANT	X-RAY THERAPY	NONE
Mathieu (28)	24	3	1	0	0
U. of M. (13)	6	0	0	4	3
Wilson (5)	2	1	0	0	2

In our cases, total hysterectomy and bilateral salpingo-oophorectomy were performed in six. The remaining 7 patients were inoperable; 4 were treated by x-ray therapy applied to the local lesion and metastases, while 3 patients received no treatment.

One of the advanced patients was admitted on the Neuro-Surgical Service with all of the characteristic signs and symptoms of brain tumor; the diagnosis was first made at the time of microscopic examination of tissue removed at time of craniotomy. One patient in our clinic who had had a total hysterectomy and a bilateral salpingo-oophorectomy for chorionepithelioma without demonstrable evidence of remote metastases was later admitted to another hospital with the diagnosis of meningovascular meningitis, and died within three days after her admittance. We can conclude, from these treated patients and untreated patients, that routine x-ray study of the chest and routine neurologic examination, along with gynecologic clinical and biologic investigation, should be performed in every suspected chorionepithelioma.

MORTALITY

Four of the 13 patients are living and well at the present time; all four of these patients were treated surgically by total hysterectomy and bilateral salpingo-oophorectomy. One of the 6 patients treated in this manner died of metastatic neoplasm two months postoperatively, and one fatality occurred as a result of acute intestinal obstruction. All of the patients with advanced cases treated by other methods, including irradiation, are dead.

TABLE IV. MORTALITY

	DEATHS	LIVING
Mathieu (28)	2	26
Brews (24)	14	10
Mahfouz (15)	3	12
U. of M. (13)	9	4
Wilson (5)	3	2

A summary of the mortality by various observers is recorded in Table IV. The survival percentages appear to be unusually high in some of the series. This information immediately raises the question of whether very early diagnosis was made in many of these cases or just how accurate was diagnosis. This point is well presented in Wilson's excellent report of 5 well-worked-up cases. In the collected series reported by Mathieu and in Mahfouz' series of 15 cases, the diagnosis was frequently made by microscopic examination of tissue only.

The interval between the time of admittance, when the diagnosis was made, and the time of death varied from one week to three months. The average interval was 1.1 months. The average interval between the date of the first symptom and the time of death was 5.7 months, with the shortest interval being three months and the longest interval fifteen months. Doubtless lives could be saved by general recognition of the fact that an early diagnosis of chorionepithelioma can be made only by careful consideration of vaginal bleeding following a pre-existing pregnancy, abortion, or mole.

The anatomic cause of death in our patients is listed in Table V.

TABLE V. MORTALITY

CAUSE OF DEATH	NUMBER OF CASES
Cerebral metastases	3
Diffuse meningeal involvement?	
Pneumonia, secondary to metastases	3
Cachexia	1
Intestinal obstruction	1

The sites of metastasis are listed in Table VI.

TABLE VI. METASTASES (NINE CASES, EIGHTEEN SITES)

SITES OF METASTASIS	NUMBER OF PATIENTS WITH THESE SITES
Lungs	5
Vagina	4
Brain	2
Liver	2
Rectum	1
Ovary	1
Diaphragm	1
Adrenals	1
Periaortic nodes	1

These sites of metastasis were found either at the time of operation, at autopsy, by roentgenographic examination, or by biopsy.

Pulmonary metastases occur by direct hematogenous embolic transmission. The mechanism of spread from the primary uterine site to the vagina most likely occurs by way of the fine interlacing of vessels between the fundus and cervix, and thence through the network of vessels common to the cervix and vagina. It is not altogether improbable that vaginal spread might also occur by systemic route in an embolic manner. Cerebral metastases, we feel, occur directly if a patent foramen ovale can be shown to be present. If this cannot be demonstrated, retrograde venous metastases, and tertiary spread from pulmonary metastatic lesions offer the more plausible explanations for this involvement. The remaining sites of metastasis occur by way of direct blood stream routes.

Lutein cysts were found in four of the patients, either at the time of autopsy or at the time of operation. In one patient in whom orange-sized lutein cysts of the ovary were found, the fluid from the cyst was studied to determine the presence or absence of gonadotropic substance.

The tests were very strongly positive. Lutein cysts did not occur with the same frequency in our group of cases as has been reported by other observers.

SUMMARY

We believe that early diagnosis of chorionepithelioma can be made only by constantly keeping the diagnosis in mind.

Of what significance is the biologic test in diagnosis? Any patient showing a positive biologic test for the luteinizing hormone four weeks after delivery of a full-term pregnancy or following an abortion, or, in whom the test remains positive for six weeks or longer following the passage of a mole presents strong evidence of an existing chorionepithelioma. While we have come to rely upon the reaction of the Aschheim-Zondek test, this test, plus clinical judgment, the evaluation of a complete history and microscopic appearance of the curettings should be used collectively rather than any one single criterion diagnosing the disease. Particularly significant is clinical judgment in evaluating the patient whose Aschheim-Zondek reaction becomes positive due to subsequent pregnancy.

What is the treatment of chorionepithelioma and what is the best way to treat this disease? On the basis of our report and of previous reports, we feel, at the present time, that these patients, if operable, are best treated surgically by the performance of a total hysterectomy and bilateral salpingo-oophorectomy.

Of what value is irradiation in the treatment of chorionepithelioma? We feel that, if diagnosis is made early enough to treat adequately these patients, surgery is the one treatment which will uniformly give satisfactory results. However, in the presence of metastases, the disease is best treated, and then probably only palliatively, by irradiation of the primary site and of the metastatic area, rather than by removal of the primary lesion in the hope that secondary metastases will disappear. The indications for surgery in this group should be limited to patients where continued and potentially fatal hemorrhage is present, as described by Wilson.

Frequent subsequent checks on operated patients' urine for gonadotropic substance should be carried out at monthly intervals during the first postoperative year, and once every two months during the second year. Where circumstances permit, it would be desirable to check these patients clinically and biologically at least twice yearly throughout life.

Routine roentgenographic examination of the chest and neurologic examination are indicated prior to operation in all patients suspected of having chorionepithelioma.

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GYNECOLOGIC TUBERCULOSIS

A BRIEF REVIEW OF THIRTY-TWO CASES, INCLUDING ONE OF TUBERCULOUS CERVICITIS

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GENITAL tuberculosis was first recognized by Morgagni while performing an autopsy on a girl of twenty years. There were no other reports until those of Raymond, Reynaud, and Senn in 1831. Koch discovered the tubercle bacillus in 1882. In the following year Cornil and Babes first demonstrated the bacilli in the vaginal discharge. Since then, a voluminous literature has grown, slowly clarifying the various issues of pathology, diagnosis, and treatment.

Gynecologic tuberculosis may be a primary infection introduced by the male. Secondary infection by the hematogenous or lymphatic routes, or by direct extension from a neighboring organ, is the more frequent. Recent experimental work has demonstrated that re-infection through the vaginal route in a previously sensitized individual can produce typical clinical gynecologic tuberculosis. All organs of the female genitals have been known to be involved. The individual lesions vary greatly in their frequency, tuberculous salpingitis being the most common. Tuberculous vaginitis and oophoritis, the occurrence of which was denied until recently, are the least common.

Gynecologic tuberculous lesions vary greatly in type. Vulvar lesions are ulcerative, scrofulodermal or lupus-like. Cervical tuberculosis, which often looks like malignancy,¹ is catarrhal, miliary, ulcerative, vegetating, or interstitial. Corporeal involvement may be miliary, ulcerocaseous, hypertrophic or interstitial, and is frequently diagnosed wrongly as adenomyosis or fibromyomatosis because of the irregular contour of the tender uterus. These patients, as a rule, show advanced endometrial and tubal infection, and other evidence of tuberculosis is usually present. Tuberculous oophoritis is diagnosed only by the pathologist. Tuberculous salpingitis is protean in its nature, and may be miliary, nodular, atrophic, hypertrophic, or caseous.

It is currently agreed that genital tuberculosis is not diagnosed pre-operatively unless it has been suspected. Pathologically, no diagnosis should be considered as certain until the tubercle bacilli have been demonstrated by any of the acceptable methods.

MATERIAL

From 1916 to 1940 inclusive, 1,600 autopsies and over 38,000 surgical specimens have been reviewed by the Department of Pathology at Mount Sinai Hospital in Cleveland. Thirty-two proved cases of gynecologic tuberculosis have been found. Six were verified at necropsy, and the

remainder had 30 gynecologic procedures by 12 operators. Patients with tuberculous skin lesions, peritonitis, perimetritis, perisalpingitis, or perioophoritis have been excluded, as have all those where no tubercle bacilli were found in the specimens after staining by the Ziehl-Neelsen method or by guinea pig inoculation.

The youngest patient in this series died of tuberculous meningitis at the age of two. Tuberculous salpingitis was an incidental finding at autopsy. The oldest patient was sixty-two years of age. The preoperative diagnosis of cervical malignancy was changed postoperatively to tuberculous vaginitis and endometritis. The average age of the entire group was 34 years. One patient was found to have tuberculous salpingitis sixteen years after tuberculous endometritis had been diagnosed by examination of the curettings. Tubal involvement was bilateral in all but one case, whereas oophoritis was always unilateral. Since complete operative procedures were done infrequently, it is difficult to determine the true incidence of organs involved. Vaginal procedures varied from dilatation and curettage to total hysterectomy and bilateral salpingo-oophorectomy. One Watkins' interposition operation and four gynecoplastic repairs were included among the vaginal procedures. Abdominally, the most radical operation was a total hysterectomy, bilateral salpingo-oophorectomy and subtotal cystectomy in a patient with uterine malignancy and incidental tuberculous salpingitis. In one patient, the operation was limited to a biopsy of the involved tissues.

The organ frequency in the specimens examined by our laboratories was:

ORGAN	SURGICAL	AUTOPSY
Tubes (unilateral once)	23	6
Endometrium	9	1
Myometrium	5	1
Ovary (always unilateral)	3	0
Endocervix	2	1
Cervix (interstitial)	1	0
Vagina	1	0
Vulva and Bartholin gland	0	0

Reports in the literature state that tuberculous cervicitis occurs about once to every 200 cervical malignancies. During this same interval, our pathologists diagnosed 201 carcinomas of the cervix uteri.

The diagnosis was made preoperatively in only 3 patients, all of whom gave a history of previous tuberculous peritonitis. Diagnosis was made at operation in 13 cases. Four patients were parous, one having borne eight children. Eight were unmarried. The preoperative diagnosis in 3 of these was ectopic pregnancy. In one, who had a tender pelvic mass and an amenorrhea of five months, the Friedman test was weakly positive. The final diagnosis was tuberculous pyosalpingitis. This was the only patient in the entire series who had missed any periods, though all but 5 complained of menstrual irregularities. Menorrhagia, with or without metrorrhagia, and associated with severe dysmenorrhea occurred in the majority. Except in those with pelvic abscesses, the disease was never suspected.

The incisions of 11 patients were not healed and still draining at the time of their discharge from the hospital. Drainage had been instituted at operation in 5 patients, and the wounds of all broke down. Two incisions were resutured, but disrupted a second time. One patient developed a rectovaginal fistula after the removal of a left tuberculous tuboovarian mass. One patient, at necropsy, was found to have a sigmoidosalpingovesical sinus which communicated with a tuberculous pelvic abscess. Death followed uremia secondary to tuberculous destruction of both kidneys. One patient developed an acute tuberculous peritonitis after her operation but recovered. One patient died within a month of her delivery of a normal term infant.

A slight to severe anemia was present in 22 of the 30 surgical cases. Nine required transfusion for blood loss during the operation or for postoperative shock and sepsis. The white blood count on admission was elevated above 10,000 per c.mm. in sixteen patients. The highest count was 23,500 in a patient with pelvic abscess. No sedimentation rates were done. Nine patients were discharged before the fifteenth postoperative day. The average hospital stay was 25.3 postoperative days, and the longest was 85 days.

Two patients later developed malignancy. The first patient died of an alveolar adenocarcinoma of the lung with generalized metastases two years after the internal genitals had been removed for tuberculosis and fibromyomas. The other, in whom a diagnosis of tuberculous endometritis had been made sixteen years previously, was operated upon for utero-cervical malignancy which involved the bladder. An active tuberculous salpingitis was found at this time. She is still alive three years after this second procedure.

Seven patients were not seen again after their discharge from the hospital, and 6 were followed for less than one year. Of the others, 6 are apparently free of tuberculosis at present. Two are inmates of sanatoria. One has pulmonary tuberculosis, and the other is recovering from tuberculous peritonitis. One patient has a laryngeal lesion which is suspected of being tuberculous. Four patients are known to have died, one of drowning, one of generalized tuberculosis, and one of carcinoma of the lung. In the fourth patient, the cause of death is unknown.

Of the 6 patients in whom autopsy confirmed the diagnosis, 2 died of uremia and pyelonephritis. One, the youngest, died of tuberculous meningitis. The fourth developed a pleurisy with effusion in the fifth month of pregnancy, delivered normally at term and came to necropsy four weeks later with an acute generalized miliary tuberculosis. The last two were classified as anesthetic deaths, dying under anesthesia for tooth extraction and cholecystectomy, respectively. The findings of gynecologic tuberculosis were incidental in each of these.

CASE REPORT

A detailed report of the most recent patient follows: A. D. (S. P. No. 35207 and 35298), negress, aged 18 years, was admitted to the gynecological service at Mount Sinai Hospital on Sept. 12, 1939. She complained of acute generalized abdominal pain associated with nausea,

colic, and occasional emesis of twenty-four hours' duration. The onset followed cessation of her last menstrual period on Sept. 10, 1939. Menarche occurred at fourteen years of age, and menses had always been regular, lasting three to four days. They were occasionally associated with lower abdominal cramps during the first day of flow. There had been a moderate leucorrhea for the past year. Promiscuity without prophylactics was admitted.

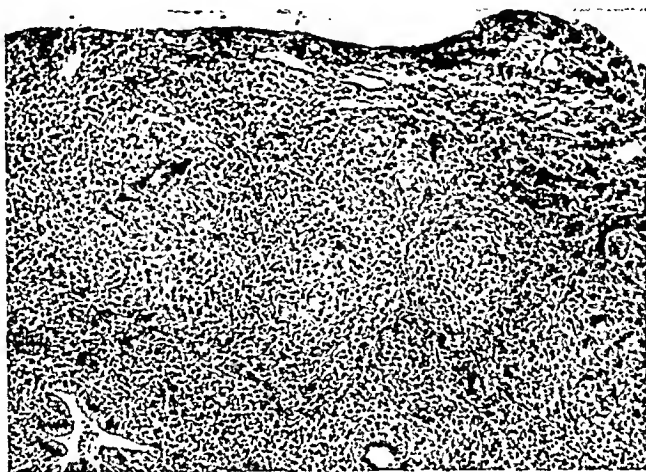


Fig. 1-A.—(S. P. No. 35298.) Tuberculous cervicitis. The surface is denuded. A cervical gland is seen at the lower left corner. The remaining tissue is not recognizable. There are areas of degeneration, tubercle formation and several typical Langhans' giant cells.

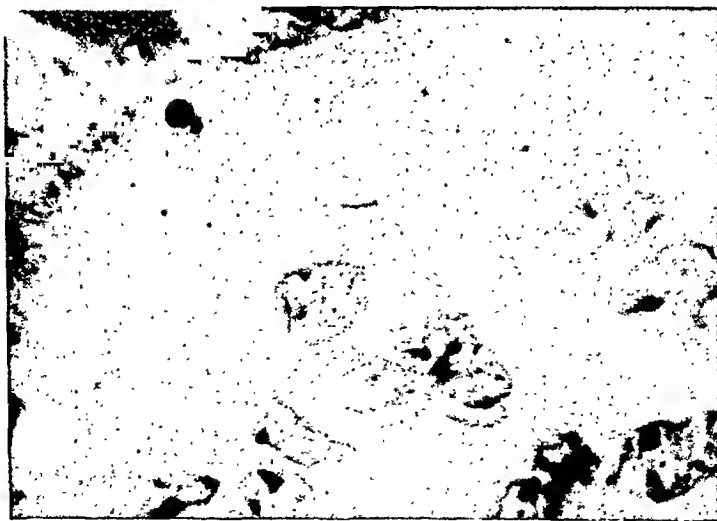


Fig. 1-B.—Ziehl-Neelsen stain showing a tubercle bacillus in one of the giant cells in Fig. 1-A.

Past history at the time of admittance was noneontributory. Later, it was learned that she had had a pleurisy with effusion in 1937. Family history showed that her sister died of pulmonary tuberculosis in 1936. At that time the patient's von Pirquet test was positive, but x-ray of the chest was reported as negative. Temperature on admission was normal, but rose to 101° F. Pulse was 110 per minute; hemoglobin,

85 per cent; the red and white counts were 4.5M and 11,400 per c.mm., respectively. A diagnosis of pelvic peritonitis was made and conservative therapy was instituted. Temperature and pulse returned to normal on the fifth day. She was discharged on the twelfth day, at which time the white count was 9,000. Internal pelvic examinations were not done.

Examination in the out-patient department on Oct. 25, 1939, revealed a left tuboovarian mass. At that time, she stated that menometrorrhagia had been present since her discharge from the hospital. A Friedman test was negative. A small cervical erosion was then treated with silver nitrate stick and foreign protein therapy was begun. Menses returned to normal by Jan. 5, 1940. However, a weight loss of fifteen

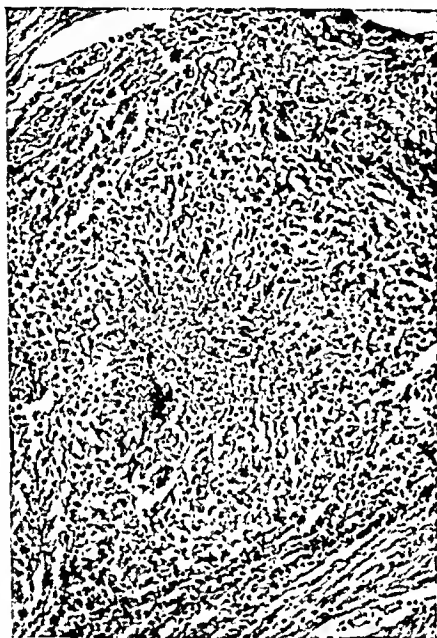


Fig. 2.



Fig. 3.

Fig. 2.—(S. P. No. 35298.) Tuberculous myometritis. Except for a few smooth muscle fibers at either end, the tissue is not recognizable, being replaced, for the most part, by a tubercle with central necrosis and giant cell formation.

Fig. 3.—(S. P. No. 35298.) Tuberculous endometritis. Endometrial glands are visible at the upper left corner. The rest of the tissue shows inflammation, necrosis, and giant cell formation.

pounds was noted. The cervix, at this visit, was found to be irregular and hypertrophied. There was a friable papillary overgrowth which covered almost half of the anterior lip. The examination caused free bleeding. The cervix was moderately fixed, and the adnexa were not palpable. Hospitalization was advised for biopsy, as a cervical malignancy was suspected and physical examination by the medical department was reported as negative. The patient entered the hospital on Feb. 15, 1940, at which time the only additional findings were an increased weight loss, a slightly larger cervical lesion and moderately increased cervical and parametrial fixation. The rest of the internal examination was unsatisfactory. Curettage of the uterus and biopsy of the cervix were done under nitrous oxide-oxygen anesthesia on the following day. Examination of frozen sections showed tuberculous cervicitis.

During the ensuing two weeks, an attempt was made to rule out other tuberculous foci. No active lesion outside of the pelvis was found. Cystoscopy, retrograde pyelograms, x-ray of the chest, and guinea pig inoculation with sputum and urine failed to disclose active tuberculosis.

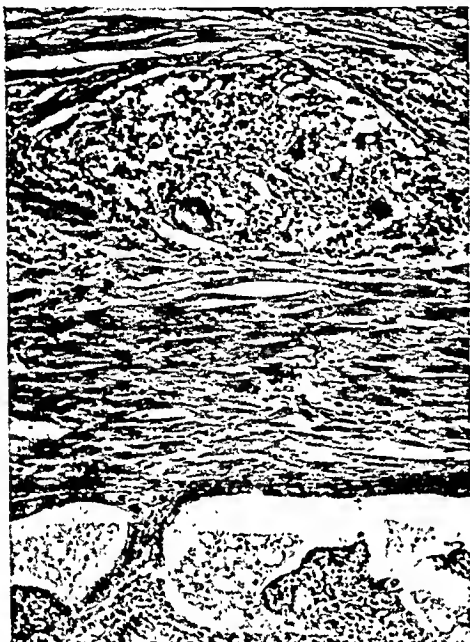


Fig. 4.

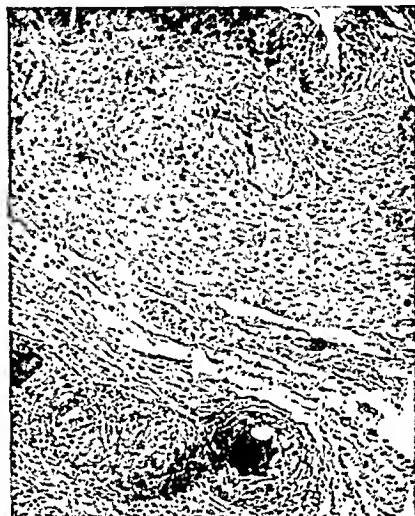


Fig. 5.

Fig. 4.—(S. P. No. 35298.) Tuberculous salpingitis (interstitial). The endosalpinx is visible at the left and shows evidence of a chronic inflammation. The myosalpinx is edematous, and at the right the muscle fibers are separated by an area of degeneration and giant cell formation. In other areas, the endosalpinx was involved, but pictures here could not be distinguished from tuberculous endometritis.

Fig. 5.—(S. P. No. 15861.) Tuberculous oophoritis. The right half shows the wall of a developing follicle. The left contains typical tuberculous inflammation and giant cell formation.

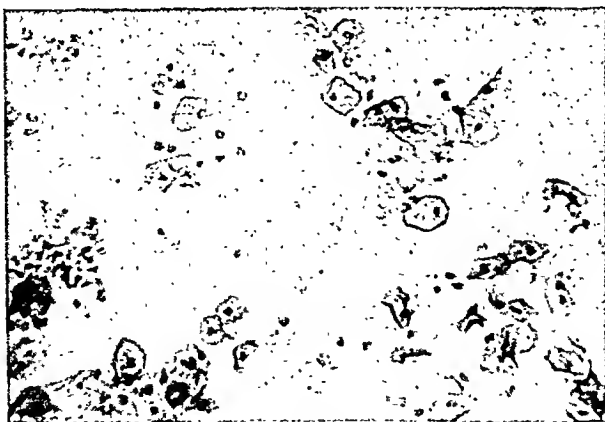


Fig. 6.—Vaginal smear after the method of Papanicolaou showing a moderate estrin deficiency. Both ovaries of this patient were totally removed one year previously. Urinary estrin-excretion at this time is over twenty rat units per day.

Despite her age, total hysterectomy and bilateral salpingo-oophorectomy were performed on March 1, 1940, under general anesthesia. The intestines were matted by old firm adhesive bands. No attempt was

made to locate or remove the appendix. The operation was easily performed after separating the adherent bowel from the uterus, tubes, and ovaries.

The pathologic diagnosis was tuberculous cervicitis, endocervicitis, endometritis, myometritis, salpingitis, perisalpingitis, perioophoritis and peritonitis; only the ovaries were uninvolved.

Her convalescence was stormy. She developed intestinal obstruction and was operated upon on March 16, 1940, at which time several bands of firm adhesions in the left upper quadrant were severed; a volvulus was relieved and an enterostomy was done. The patient was discharged on May 8, 1940, after closure of the enterostomy. The midline incision had healed by first intention, and the enterostomy wound was granulating but not draining. She was readmitted on May 12, 1940, with a recurrence of intestinal obstruction following an unwise meal. This was easily relieved by the Miller-Abbott tube and enemas. She was well within ten days but was not discharged until June 4, 1940, at which time she weighed 84 pounds. The combined hospital stay was 106 days. She is now well, weighs 112 pounds, and has returned to normal activity.

There was evidence of surgical menopause after the pelvic laparotomy, but there have been no flushes for the past six months. Vaginal smear after the method of Papanicolaou, done on April 16, 1941, showed only a moderate estrin deficiency. Estrin excretion studies show 20 R.U./24-hour specimen of urine.

There is a slight incisional hernia at the enterostomy site. Re-examination of the surgical specimen disclosed that both ovaries had been totally ablated. The probable source of the estrin now being excreted is either the adrenal glands, or aberrant ovarian tissue.

COMMENT

The question of surgical intervention in this case was not clear at first. Several local internists suggested surgical intervention if no other active lesion was present. Of current literature, only the monographs by Norris³ and Jameson² were of help. Both authors give evidence supporting radical as well as conservative treatment, but prefer the former if active tuberculosis is not present elsewhere. Both state that insufficient data are at hand for a critical evaluation of the various types of therapy. Jameson's work is the most recent, and I quote excerpts which influenced our decision.

On page 68 (et. seq.), he writes: "... failed to find a report of spontaneous healing of tuberculosis of the cervix . . . and untreated cases of ulcerative and papillomatous tuberculosis of the cervix tend to progress." "Curettage has been employed with good results, but the method is condemned . . . because of the danger of dissemination of the disease." "If tuberculosis of the upper tract is recognized pre-operatively, and biopsy of the cervix is positive, one is justified in doing a total hysterectomy." Later he states: "Roentgen-radiation in cervical tuberculosis has failed to give favorable results . . . and it is self-evident that radium could have but little effect in the presence of large caseous masses. . . ." Of adnexal and uterine tuberculosis (page 131, et seq.) he states: "Experience has shown that cases of tuberculous salpingitis treated by the usual conservative measures employed in common tubal inflammations fail to regress . . . but is the only method

justified in certain cases with the possible exception of simple laparotomy or roentgen-ray therapy." In regard to surgery, he comments: "... it is absolutely impossible to determine the extent of the disease macroscopically . . . and bilateral salpingectomy should be done. . . . If . . . removal of the ovaries has been necessitated by extensive adnexal disease, there is no particular value in leaving the uterus in situ. It has been shown . . . that the danger of producing untoward symptoms of premature menopause in young women by oophorectomy is less than in other types of pelvic disease because the internal secretion of the ovary has already been suppressed. . . ."

SUMMARY

The history and pathology of gynecologic tuberculosis have been briefly reviewed. Surgical and autopsy records of 32 patients affected with gynecologic tuberculosis at Mt. Sinai Hospital in Cleveland have been summarized, and the case histories reported. There was no immediate operative mortality. Thirteen patients have not been followed. Four are known to be dead, one with tuberculosis. Six, and possibly 7, are living and apparently free of the disease, while two have active, nongynecologic tuberculosis. The pelvic findings were incidental in 5 of the 6 diagnosed at autopsy. The sixth died one month after delivery. Preoperative diagnosis was seldom correct, and most patients had a septic postoperative course. All drained incisions disrupted, and almost half of the patients left the hospital with draining wounds. Except for a history of menometrorrhagia, dysmenorrhea, and relative sterility, gynecologic history was not typical. A case of an 18-year-old negress with extensive pelvic tuberculosis, who was treated by radical surgery, with apparent recovery, is reported in detail. Various methods of treatment of gynecologic tuberculosis are presented.

I acknowledge the permission to review the case histories summarized above, and express my gratitude to the surgeons who gave that permission. I wish to thank Dr. Kline and his associates in the laboratory for their assistance, particularly Miss Josephine Jones who stained and isolated the tubercle bacilli, and Mr. Wm. Stevenson who photographed the slides.

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3. Norris, Chas. C.: *Gynecological and Obstetrical Tuberculosis*, Vol. XI, Appleton's *Gynecological and Obstetrical Monographs*, 1931.

FURTHER STUDIES ON THE STERILE AND FERTILE PERIODS IN WOMEN

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THE so-called "safe" period is of special importance for those women who, because of "conscientious objections" or otherwise, would not resort to chemical or mechanical contraceptive measures; and likewise for all those who, on account of esthetic reasons or practical considerations, such as interference with normal sensations or fear of injury to physical or mental well-being, would object to the use of artificial contraceptives.

Because of the pioneer work of two investigators in this field, the safe period principle has been generally known as the "Ogino-Knaus" theory. As explained at length in earlier publications, it proposes the following basic claims under normal conditions:

1. Ovulation occurs fourteen days before menstruation.
2. The life span of the corpus luteum is fourteen days.
3. The ovum is subject to fertilization for only a few hours after its expulsion from the Graafian follicle.
4. The male sperm, within the female genitalia, can fertilize the ovum only within a limited period of time, lasting not more than forty-eight hours.

Although within the last few years many papers have been published containing such statements as, "the safe period is not safe" or, "the safe period is only approximately safe," etc., we have yet to find a controlled report on several hundred women with written records of their menstruations and coitus which serve to prove the validity of the claims of "Rhythm" babies. Memory records, as so often pointed out, are notoriously faulty, and unfortunately many women receive the wrong information based upon the old Capellman theory or upon an erroneous conception of the method under discussion.

Many couples making use of the "safe period" during the past few years have kept accurate written records of the dates of the beginning of their menstruations, of the actual dates of cohabitations, and of the various extrinsic factors which might have led to disturbances in ovulation and the normal functioning of the corpus luteum. We were gratified by the intelligent cooperation of most of our patients. The analysis of their reports, received from July, 1937, to June, 1940, form the basis of the present communication. Most of this material is graphically outlined in three charts.

Chart 1 depicts the records of 24 women who at first used the sterile periods to avoid pregnancy and later cohabitated in the fertile periods and conceived.

The figures in the first horizontal line of each case indicate the number of cohabitations that took place on the listed days of the cycle, none of which resulted in a pregnancy. The figures in the column under the heading "months" indicate the number of months the method was used according to available records. The figures headed "total" refer to the number of cohabitations which occurred during the sterile periods while conception was to be avoided.

CASE NO.	CYCLE NO.	MONTH	DATE OF BEGINNING OF MENSES	DAYS AFTER BEGINNING OF MENSES																																TOTAL	ADDITIONAL DATA																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
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221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421

menses did not occur until Jan. 20, 1937. This resulted in an extraordinary fifty-one-day cycle and is probably attributable to the influenza. In the menstrual month beginning Jan. 20, 1937, there were four cohabitations within the fertile period, namely on the seventh, eighth, ninth, and tenth days of the cycle, during which time this woman conceived; the baby was delivered on Oct. 23, 1937.

Case 14 presents unusual features. In the menstrual month beginning Nov. 30, 1936, coitus took place on Dec. 16, which was the fifteenth day before the onset of the next menses (December 31), yet conception failed to occur. The change of climate, experienced between December 14 and 25, might conceivably have prolonged the life span of the corpus luteum to more than the conventionally accepted fourteen days, if we assume that ovulation occurred before December 16. The climate change during the first part of July, 1937, might explain why no conception occurred on the sixteenth, eighteenth, and nineteenth days of the cycle (July 19, 21, and 22), during the menstrual month beginning July 4. Ovulation probably occurred before July 19. In the menstrual month commencing Sept. 27, 1937, there was no conception because intercourse took place on the day following ovulation; likewise, in the menstrual month commencing Oct. 24, 1937, the woman had intercourse on the assumed ovulation day, yet menstruation occurred November 22. In the subsequent menstrual month there was evidently a fertile intercourse and a child was born on Sept. 7, 1938.

Cases 16, 17, 18, and 20 may be interpreted in a similar manner.

In summary, Chart 1 indicates that cohabitations executed during the sterile periods do not cause pregnancy, whereas intercourse properly timed and executed during the fertile period eventually results in conception if male and female are fertile.

When we review the ten cases, 25 to 34, appearing on Chart 2-A, we find that with the exception of Case 30, all these women had borne one or more children at one time or another, and we may assume therefore that nine of these women are probably fertile. Because of some disturbing extraneous influence, there was a delay in menstruation in Cases 25 to 31 and in Case 33. When we notice, especially in Cases 26, 28, 30, and 31, the time of the intercourses preceding these delayed menstruations, we wonder why pregnancy did not result since copulation took place on or about the fifteenth day before the onset of menstruation. We might enter the realm of conjecture and postulate anovulatory menstruation, temporary sterility, or a prolongation of the life span of the corpus luteum, due to the upsetting factors, as mentioned under "additional data." The latter assumption probably approximates the actual facts.

By the same process of reasoning, one might assume that physical or mental strain, as well as other disturbing factors, such as physical or mental shock, unusual exertion, change of climate or altitude, certain medication, etc., could shorten the accepted viability of the corpus luteum as demonstrated in Cases 32 and 34.

If the women representing Cases 25, 26, 27, 30, and 32 intended to avoid conception, and to all appearances this seems to have been their intention, then these cases illustrate the typical faulty application of the method. There was no assurance that ovulation had taken place when the extraordinary event, which apparently resulted in a disturbance, had occurred or began to occur. The particular extraordinary event might have delayed ovulation and abstinence should have been practiced until

the disturbance had passed and until the menstrual cycle which might have been affected had terminated. For instance, in Case 25 an automobile accident occurred on July 11, which was the fifteenth day of the cycle and as ovulation might have been considerably delayed, this woman should have abstained until the beginning of the next menses. This is particularly true if she did not want to take any chances of becoming pregnant.

In summary, Cases 25 to 34 seem to show that temporary disturbances of various character delay or hasten the function of the corpus luteum as well as the onset of the next menstruation.

No. 2-A

EXTERNAL INFLUENCES WHICH APPARENTLY DISTURB OVULATION & THE NORMAL LIFE-SPAN OF THE CORPUS LUTEUM.

[illegible]

No. 2-B

FERTILE PERIOD = []

COHABITATIONS = X

MENSTRUATION = M

Chart 2.

Chart 2-B illustrates the only two involuntary pregnancy cases in our files of which satisfactory written records are available; however, even these records are not entirely complete. It should be stated that besides these two cases, we were informed of 26 additional undesired pregnancies. From the information which we could extract, it is apparent that the great majority of these 26 additional cases were caused by faulty application of the method, the use of contraceptives or the practice of retractions during the fertile period.

The woman represented in Case 35 became pregnant while cohabitating outside of the fertile period, as established by a record kept for eighteen months prior to February, 1937, when she was seeking advice regarding natural conception control. As she was underweight and as a secondary anemia was suspected, she was instructed to consult her family physician for her blood condition and, if necessary, have a blood count made. This examination was made and found negative; however, it was revealed that an anemia existed in 1933.

Although the patient was warned against practicing natural conception control during the recurrence of the secondary anemia and al-

the number of times these cycles occurred. Correspondingly, in Column 1, we listed the number of women who had experienced these cycles. For example, 342 women recorded a thirty-day cycle 784 times; these same women, of course, had other cycles listed elsewhere. In the body of the chart are recorded the number of intercourses had on the various days of the cycle. Ovulation is shown by a black dot. For example, the 223 women who had a twenty-four-day cycle 724 times, had ten cohabitations on the second, 32 cohabitations on the third, 78 cohabitations on the fourth, etc., days after the onset of menstruation. All told, there are 11,249 cycles listed, with 49,356 intercourses, and conception failed to occur.

Chart 3 furnishes the practical proof that ovulation must occur about as shown, that the time for fertilization of the ovum is very short, and that the life of the sperm cells inside the female genitals is limited to less than forty-eight hours. If this were not the case, a number of pregnancies should have occurred, as it cannot be assumed that a higher than average percentage of the couples who furnished the data for this chart are sterile.

In addition to the 4,702 cohabitations executed by 114 couples and reported in the *Journal of the American Medical Association*, Oct. 19, 1935, and the 11,222 cohabitations of 265 couples published in the *Illinois Medical Journal*, March, 1937, we have reported in this paper, 54,027 cohabitations which were executed during the sterile periods, listed in Charts 1 to 3, giving further evidence that abstinence during the fertile period prevents conception.

CONCLUSIONS

This factual evidence confirms our belief that the biologic law of sterility and fertility as originally propounded by Knaus is correct, essentially practical and workable.

209 SOUTH STATE STREET

Escomel, Elmundo: Therapy of Enteritis, Vaginitis, Cystitis and Gingivitis Produced by Trichomonad Infestations, *Presse méd.* 48: 172, 1940.

The writer, a Peruvian physician, states that trichomonad cases are observed rarely in Europe. He observes that this type of protozoan infestations is frequent in colonial French Africa, Asia, and in the three Americas. In the subtropical and tropical Americas the incidence of trichomonad infestation is regarded as even greater. These statements are not supported by statistical data.

For vaginal trichomonorrhea the author recommends two daily douches with 1:1,000 solution of oxyeyanide or a 1:4,000 solution of potassium permanganate. Each irrigation is followed by drying the vaginal canal and leaving a tampon, soaked in Franck's emulsion, a mixture of turpentine, laudanum and gum syrup. The medicated tampon is used twice daily for a period of three days. The vulva and vestibule are protected by vaseline and a vulvar pad.

Relief from vesical trichomoniasis is obtained by daily instillations of this emulsion into the bladder, without previous lavage. This is done for three days.

CLARE E. FOLSOME.

A CLINICAL AND PATHOLOGIC STUDY OF 115 CASES OF TUBAL PREGNANCY

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THIS communication is a study of 115 patients with tubal pregnancy operated upon at the City Hospital, Welfare Island, New York City, from 1922 through 1939. The clinical conclusions correspond in the main to generally accepted concepts, though in two respects they differ from prevailing views. First, the duration of amenorrhea seemed to depend more on the type of implantation than upon its site. The erythrocyte sedimentation rate was not found entirely reliable in differentiating pelvic inflammatory disease from ectopic pregnancy. The histologic examinations led to conclusions very different from the more accepted views. The cause of ectopic pregnancy could not be determined from the condition of the tube in a great number. Decidual reaction was very common and appeared to be a response to the chorionic villi present and to their state of preservation.

Since the clinical data were obtained from the hospital records, the composite work of attending and resident staffs over a long period, the observations and interpretations showed variations due to the changing concepts year after year. Conclusions in this study were made bearing this factor in mind.

The ages ranged from 19 to 38 years, the average being 29. Sixty-eight, or 59 per cent, were between 25 and 34 years. These data correspond closely to those of Schumann.¹ He reported 60 to 70 per cent of ectopic pregnancies occurring between 24 and 33 years. Fitzgerald and Brewer² reported a case in a woman 49 years old. In Darley's³ case, the patient was only 12. We did not find these extremes in our series.

Ectopic pregnancy occurred in 71 white and in 39 colored women, a percentage of 64.5 and 35.5, respectively. It is impossible to state whether this represents a true proportion since the ratio of colored to white patients admitted to the service for the period studied is not available. However, Langman and Goldblatt⁴ reported that at Bellevue Hospital, where 40 per cent of the gynecologic patients were colored, only 11 per cent of the total ectopic pregnancies were found in this group. These data strongly suggest that the white race is the more prone to develop this condition.

There had been previous pregnancies in a high percentage of the cases. Eighty-five patients, or 77 per cent, had normal uterine pregnancies preceding the tubal gestation. The number of pregnancies ranged from 1 to 8 and the average was 2.8. It was noteworthy, however, that 48.3 per cent of the multiparas had a period of sterility of three years or more between the last uterine pregnancy and the ectopic gestation. Thus despite a high degree of fertility in the women who developed ectopic pregnancy, a sterile period preceded the abnormal pregnancy in about half the cases.

The one constant symptom was pain, which was presented in all of the 115 cases. Grier,⁵ Fitzgerald and Brewer, and Rieci and Di Palma⁶ also emphasized the importance of pain as a constant finding. The character of the pain varied according to the pathologic process. In the cases of ruptured tube, the pain was frequently sharp, at times cramplike, but almost never dull. It was usually generalized or in the lower abdomen, severe, more often continuous than intermittent, referring occasionally to the shoulder and less often to the rectum. The tubal abortions were accompanied by pain resembling that seen in uterine abortions, cramplike rather than sharp, intermittent, severe and lower abdominal. The unruptured tubal gestations had sharp intermittent pain. Falk⁷ states that pain is due to distention of the tube by hemorrhage and is not the result of pressure from a growing ovum.

Menstrual disturbance was the next most common symptom, occurring in 113 of the 115 cases. The disturbance was usually a period of amenorrhea followed by vaginal bleeding. Vaginal bleeding was present in 97 and amenorrhea in 92 cases, either singly or together. The bleeding was described as "profuse," "spotting" or "mixed with clots." No one type was constant either in rupture or in abortion. It was noted, however, that in unruptured gestations the bleeding was often described as "scant and dark brown." It is unlikely that a true history of missed period or abnormal bleeding was always obtained, because patients will frequently call the "spotting" a normal period if it occurs at the time a period is expected.

There was no demonstrable relation between the duration of amenorrhea and the site of nidation in pregnancies which terminated by rupture. The duration was 51.6 days in the interstitial, 53.7 in the isthmie, and 51.5 in the ampullary pregnancies. These findings were contrary to the generally accepted belief that cases of isthmie gestation rupture earlier than the interstitial or ampullary types.

A significant difference was found in the length of amenorrhea in the abortions, and it is the belief of the authors that this difference depends mainly upon the type of nidation. In the abortions the duration was 40.5 days, in ruptures 52.2 days, and in unruptured pregnancies 53 days. It is generally accepted that the type of nidation, whether luminal or mural, determines the pathology which follows. In luminal

implantation, the pseudocapsularis is notoriously weak and prone to early rupture. This fact probably is the underlying factor in the shorter duration of amenorrhea in abortion.

The less common symptoms were recorded only when present. Vomiting was noted in 30 cases, fainting in 25, nausea and weakness each in 19 and dysuria in 8. Indications of pregnancy aside from amenorrhea were decidedly infrequent. Only 4 patients had morning sickness and 3 had swollen breasts.

The most common sign obtained by abdominal examination was tenderness, which was found in 88 cases. Other findings were less frequent. Rigidity was present in 32 cases, rebound tenderness in 29 and distention in 12. It is likely that distention occurred more frequently than indicated in this series, and that Falk was correct when he stated that "abdominal distention is a very frequent sign that is overlooked."

Palpable masses on pelvic examination were as frequent as abdominal tenderness. They were adnexal in 64 cases, cul-de-sac in 13, and combined cul-de-sac and adnexal in 11 cases. When masses were found in the cul-de-sac, the clinical evidence pointed to repeated small hemorrhages. These probably led to periodic increases in blood clot organization and tumor formation. With a single massive hemorrhage, surgical procedures were carried out too early to permit masses to form. The isthmic gestations particularly seemed prone to be associated with single large hemorrhages.

Cervical changes were found less frequently than pelvic masses. The cervix was tender on motion in 39, soft in 30 and blue in 6 cases. Quite frequently more than one change was seen in the same cervix.

Diagnostic colpotomy was performed in 9 cases. Free blood was found in 8 while all cases were ruptured. The value of this procedure seems doubtful. A negative result does not disprove the presence of ectopic pregnancy. Furthermore, Grier reported a long stormy convalescence following its use.

Diagnostic curettage was performed in 9 cases. A decidual reaction of the endometrium was found in 5, a proliferative endometrium in 3 and a menstrual endometrium in 1. In the last four, rupture had occurred some time previously. The report "decidual reaction, no chorionic villi seen," while suggestive of ectopic pregnancy, is not pathognomonic. A decidual reaction alone may be found in a high percentage of curettages in cases of incomplete abortions. Nor does the absence of a decidual reaction eliminate the diagnosis of ectopic pregnancy. In an ectopic pregnancy which has ruptured a few weeks before the patient is admitted, the uterine decidua may have been cast off and replaced by a proliferative endometrium. The curettage is of definite value only when chorionic villi are found, which show that the case is definitely one of intrauterine pregnancy.

Leucocyte counts, done in 83 cases, showed a range of 5,800 to 28,000. In the abortions and ruptures, the average counts were approximately the same, 11,950 and 12,720, respectively. A few patients with rupture had normal counts, when the rupture had occurred a month or more previously. The unruptured gestations had counts on the average only slightly lower, 10,480. The differential blood picture was of more significance than the total counts. In rupture, the average neutrophilic percentage was 80.5; in abortion 67.7. The unruptured cases were too few to permit the drawing of any conclusions. Changes in the leucocyte counts appeared to be more closely related to the presence of initial intraperitoneal hemorrhage than to the pregnancy. Ricci (1931) also suggested this interpretation. He found an initial leucocytosis occurring at the time of intra-abdominal spill, followed by a gradual decline. In the present series repeated counts were not done. However, it seems evident that the gradual fall in a ruptured ectopic pregnancy differs from the persistent leucocytosis of inflammatory disease.

Erythrocyte counts and hemoglobin determinations were done in 93 cases. The red blood cell counts ranged from 800,000 to 5.5 million; the hemoglobin percentages from 20 to 100 per cent. In abortions, the average red cell count was 3.67 million and the average hemoglobin 62.7 per cent. In rupture they were 3.1 million and 58.5 per cent. These determinations proved of value as an indication of blood loss.

The erythrocytic sedimentation rate was estimated in 80 cases by the Linzenmeir method. Sixteen cases, or 20 per cent, had a rate of thirty minutes or less. Urdan⁸ had identical findings in 44 cases. In a group of 30 cases, Tenney⁹ found 10 per cent with a rapid rate. The increased sedimentation rate appeared to be due to the pregnancy itself in the majority of instances. Acute salpingitis was found in only two cases. In the other 14, neither the pathologic data nor the clinical findings revealed any inflammatory disease which could have been responsible. The degree of anemia did not offer an adequate explanation. The average red cell count was 3.1 million and the average hemoglobin 56.7 per cent. In 64 cases with sedimentation rates above thirty minutes, the corresponding figures were 3.2 million and 64 per cent.

Friedman tests were carried out in 11 cases. Eight were positive and 3 were negative. In the latter, clinical evidence indicated that rupture had probably occurred a month or more previously. Furthermore, the histologic examinations revealed markedly degenerated chorionic villi, apparently incapable of secreting the anterior pituitary-like substance responsible for a positive result.

The site of pregnancy as determined at the operating table was tubal in 93 per cent, secondary abdominal in 3 per cent, ovarian in 2 per cent, and unidentified in 2 per cent. The ovarian pregnancies proved on further laboratory examination to be secondary implants and not primary ovarian gestations. Of the 115 cases, 65.3 per cent were ampullary,

23.4 per cent isthmie, and 6.3 per cent interstitial. In this series, the incidence of interstitial implantation was higher than most observers have reported. Solomons¹⁰ found 2.3 per cent among 183 cases. Among 3,982 cases collected from the literature by Wynne,¹¹ there were 1.5 per cent. In the 278 cases of Puetz¹² there were 2.4 per cent. Rupture occurred in 79.6 per cent, abortion in 14.9 per cent, and 5.5 per cent were unruptured.

There was practically the same incidence of ectopic pregnancy on each side. The right was involved in 59; the left in 52. Lavell¹³ and Urdan found that previous surgery had a tendency to localize the pregnancy to the side on which the surgery had been done. In the present series, this did not hold true. Previous lower abdominal operations had been performed in 17 cases, among which were 12 appendectomies. Left- and right-sided gestations were equally distributed among the latter.

Histologic sections of 101 cases were available for restudy. Serial sections were not done. Six cases had slides only through the site of implantation. In the remaining 95, other portions of the tubes had been sectioned. Fifty-eight tubes were perfectly normal except for the local changes at the site of implantation. There was evidence of salpingitis in 37, of which 25 cases were classified as intense and 12 as mild. Chorionic villi were present in 83. They were well preserved in 32, slightly degenerated in 9, and greatly degenerated in 42. Decidual reaction was found in 43. It was always patchy and abortive and never very extensive. In 36 of the 43 cases where a decidual reaction was found, the chorionic villi were fresh or only slightly degenerated. These observations suggest that the presence of decidual tissue may depend upon hormones secreted by the chorionic villi, and that at the point of implantation a deciduallike reaction probably occurs in a high majority of cases.

The type of imbedding could be determined in only 15 instances. It was mural in 9, luminal in 5, and combined luminomural in 1. At no time was endometrial tissue seen at the site of nidation. An intact fetus was found in 8 cases. Embryonic parts were present in a blood clot in one instance.

Investigations centered on the Fallopian tube in an attempt to find an explanation for the occurrence of ectopic pregnancy have not led to universally accepted conclusions. Falk believes that preceding tubal disease is the deciding factor. In his series, he found evidence of previous or existing disease in 90 per cent of the cases and holds that this high incidence proves a causal relationship. In the present series and in other series reported in the literature, such a high incidence has not been encountered. Tubal disease, however, may account for a certain number. Frankel advanced the theory that nidation occurs in a focus of ectopic endometrium and that the amount of this ectopic tissue

capable of undergoing decidual reaction determines the fate of the gestation. The present authors agree that decidual reaction is almost constantly present. However, none of the cases of the present series definitely showed an endometriosis of the tube, and in fact very rarely have the authors seen it in nonpregnant tubes removed for other causes.

Perhaps a more fertile field for investigation would lie in the study of the ovum itself. It has been pointed out by many observers that the fetus of an ectopic pregnancy frequently shows abnormalities. No findings in this series bear out this theory.

The admission diagnosis was correct in 54.3 per cent and incorrect in 45.7 per cent. In the latter, the patients were admitted for salpingitis (29 cases), uterine abortion (11 cases), appendicitis (5 cases), and ovarian cyst (5 cases). However, a correct preoperative diagnosis was made in the great majority of cases after a suitable period of observation. In only a small number was a correct diagnosis made only at operation.

A postoperative morbid course occurred in 14 cases. The complications were pneumonia 3, pulmonary infarction 2, pyelonephritis 2, peritonitis 2, abdominal wall abscess 1, fecal fistula 1, evisceration 1, and severe shock 1. Five patient died, a mortality rate of 4.3 per cent. The causes of death were secondary abdominal hemorrhage, postoperative shock, peritonitis, pneumonia, and cerebral embolism. The mortality rate of this series corresponds closely to those reported by others. In a survey of 3,314 cases collected from the literature by Woodhouse,¹⁴ the mortality rate was 4.46 per cent, almost identical to that of this series. It is of interest to note that during the last six years, although many more cases were observed than in any previous six-year period, there were no fatalities. Two factors appeared responsible: the establishment of a blood bank and the use of cyclopropane anesthesia.

SUMMARY AND CONCLUSIONS

A study of 115 cases of tubal pregnancy is reported. In the main, clinical conclusions agree with generally accepted concepts. The condition occurred more frequently among white women than among colored. About 75 per cent of the patients had previous normal intrauterine pregnancies. A sterile period of three years or more occurred in about half the multiparas prior to the ectopic pregnancy. Symptoms of pain and some menstrual disturbance, usually amenorrhea followed by vaginal bleeding, were present in almost every case. The character of the pain varied with the pathologic process. The duration of amenorrhea appeared to bear no relation to the site of nidation but instead appeared to be related to the type of imbedding. Abdominal and pelvic examinations gave valuable data. Diagnostic colpotomy and curettage were of doubtful value. The erythrocytic sedimentation rate was not

entirely reliable in differentiating pelvic inflammatory disease from ectopic pregnancy. Interstitial pregnancies were found in a relatively large percentage. Previous lower abdominal operative procedures were not found to influence the location of the pregnancy. A decidual reaction of the endosalpinx was present in a large number. The theories advanced thus far to explain the occurrence of tubal pregnancy seem inadequate. It is suggested that the study of the ovum may be a field worthy of investigation.

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THE INHIBITION OF LACTATION DURING THE PUERPERIUM BY METHYL TESTOSTERONE

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A CONSIDERABLE number of reports have been made concerning the post-partum inhibition of lactation by the administration of hormones and similar substances.

In view of the excellent reports on the intramuscular use of testosterone propionate,¹⁻⁵ the following study was undertaken to determine the effectiveness of the orally active methyl testosterone.*

As has already been pointed out,¹ the inhibition of lactation in the post-partum woman is almost always a painful process. Testosterone injections have afforded a safe and effective method of greatly alleviating the soreness, congestion, secretion, and malaise that so often accompany the process of "drying-out." The convenience of such a method is obvious to patient and physician.

*We are indebted to Dr. L. Pirk and the Roche Organon Co., for their generous supply of methyl testosterone tablets (Neo-Hombreol (M) Tablets).

During the period of gestation the breasts have been prepared for lactation by the large amounts of estrogenic and corpus luteum hormones in the circulating blood stream. Actual lactation, however, seems to be initiated by the pituitary lactogenic factor (prolactin, Riddle).

Immediately after delivery the concentration in the blood of these ovarian and placental hormones drops abruptly and apparently releases the inhibition on the above lactogenic factor. Within forty-eight to seventy-two hours the breasts fill up with colostrum and then with true milk.

If, however, the lactogenic factor can be inhibited during the early puerperium, the actual flow of milk can be cut off at the fount. The normal breast congestion and secretion can, therefore, be either completely eliminated or reduced to a transient minimum. Increased comfort for the patient, reduced possibility of breast complications and less nursing care will be the result.

METHODS AND RESULTS

Twenty-five cases were selected for the test. They included ward and private cases from the Sloane Hospital and Vanderbilt Clinic and in each case it had been decided, for medical or psychological reasons, that lactation be terminated. Wherever possible, a multipara was chosen so that the patient might offer her comparison between the present methyl testosterone therapy and any formerly used method of drying up of her breasts. For the most part these women all gave histories of difficulties with lactation in their earlier puerperia. Such difficulties varied from simple congestion to lactorrhea, mastitis, and breast abscesses.

When given intramuscularly, it was found that 100 mg. of testosterone propionate given in 4 divided doses of 25 mg. each, over a period of forty-eight hours was usually sufficient to inhibit lactation and to afford relief to the patient.

The patients included in this study received from 100 to 350 mg. of methyl testosterone in divided doses. In most cases the administration was started between thirty and forty-eight hours after delivery.

Except for a loosely applied breast support no additional therapy was given. Tight breastbinders were abolished and there was no restriction of fluids, milk, cream, or butter. No purging with epsom salts was ordered and neither ice caps nor sedatives were required.

The effectiveness of the treatment was judged by the amount of breast congestion, secretion, and discomfort. The results are summarized in Table I.

Those cases in which there was complete inhibition of colostrum and milk and neither congestion nor discomfort were rated as "excellent." Those where secretion of colostrum, but no milk, was observed, with transient congestion and discomfort not lasting more than twelve hours, were called "very good." Cases where secretion, congestion and tenderness were moderate and persistent for more than thirty-six hours after cessation of medication were rated as "fair," and those where secretion, congestion and discomfort were marked and persistent for more than forty-eight hours after the administration of the last dosage were deemed "poor."

TABLE I. SUMMARY OF RESULTS

CASE	PREVIOUS LACTATION HISTORY	TIME OF TREATMENT AFTER DELIVERY	METHOD OF TREATMENT ON FIRST DAY	SECOND DAY OF TREATMENT	TOTAL DOSAGE	CHARACTER OF PUERPERIUM	RESULT
1	Mastitis and breast abscesses with previous pregnancy	4 days	50 mg. q. 3 h. for 4 doses	30 mg. q. 4 h. for 3 doses	290 mg.	Mild congestion, tenderness. Scant secretion during course of medication. Complete relief 48 hours after last administration of methyl testosterone	Good
2	Multiple breast abscesses with previous pregnancy	24 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion, tenderness. Scant secretion during course of medication. Complete relief 24 hours after last administration of methyl testosterone	Good
3	Mastitis and breast abscess	30 hours	40 mg. q. 3 h. for 4 doses	30 mg. q. 3 h. for 3 doses	250 mg.	No secretion, pain, or congestion at any time	Excellent
4	Bilateral mastitis and lactorrhea for one year	12 days	40 mg. q. 3 h. for 4 doses	35 mg. q. 3 h. for 3 doses	300 mg.	Secretion, congestion, and pain reduced by 50 per cent by end of first day of treatment; 75 per cent less by end of second day. Complete relief 24 hours after last dosage	Excellent
5	Primipara	72 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Congestion, secretion, and pain moderate at onset of treatment. Reduced by 75 per cent 24 hours after last dosage. Complete relief 48 hours after last dosage	Good
6	Moderate congestion and pain with previous pregnancy	35 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during two days of treatment but no secretion. Complete relief 48 hours after last dosage	Good
7	Primipara	36 hours	40 mg. q. 4 h. for 5 doses	None	200 mg.	Mild congestion and secretion during treatment. Complete relief 24 hours after last dosage	Good

8	Moderate congestion and pain with previous pregnancy	34 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate secretion, congestion, and discomfort persisting for 3 days after last dosage	Fair
9	Moderate congestion and pain with previous pregnancy	8 days	50 mg. q. 3 h. for 4 doses	None	200 mg.	Marked secretion, pain and congestion from third to eighth post-partum day. Complete relief 36 hours after last dosage	Excellent
10	Primipara	36 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	Slight congestion during dosage. Never any secretion or pain	Excellent
11	Moderate congestion and pain with previous pregnancy	35 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	No secretion, pain or congestion at any time	Excellent
12	Primipara	72 hours	50 mg. b.i.d.	None	100 mg.	Moderately severe congestion, secretion, and pain persisting for one week after treatment	Poor
13	Mastitis after previous delivery	36 hours	50 mg. q. 3 h. for 4 doses	None	200 mg.	Slight congestion during dosage. Never any pain or secretion	Excellent
14	Moderate congestion and pain after previous delivery	5 days	50 mg. q. 4 h. for 3 doses	None	150 mg.	Full secretion with congestion and tenderness at start of dosage; 75 per cent relief 48 hours after last dosage. Complete relief in 72 hours	Good
15	Moderate congestion and pain after previous delivery	36 hours	50 mg. q. 4 h. for 3 doses	30 mg. q. 4 h. for 3 doses	240 mg.	Mild congestion during treatment. Never any secretion. Complete relief 36 hours after last dosage	Excellent
16	Severe congestion and pain after previous delivery	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during treatment. Never any secretion. Complete relief 24 hours after last dosage	Excellent
17	Primipara	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Mild congestion during treatment. Sudden congestion and scant secretion on 6th day after treatment, lasting only 8 hours	Good

TABLE I—CONT'D

CASE	PREVIOUS LACTATION HISTORY	TIME OF TREATMENT AFTER DELIVERY	METHOD OF TREATMENT ON FIRST DAY	SECOND DAY OF TREATMENT	TOTAL DOSAGE	CHARACTER OF PUERPERIUM	RESULT
18	Mastitis after previous delivery	36 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate congestion. Secretion and pain for 3 days after treatment	Fair
19	Primipara	42 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Never any secretion, congestion, or pain	Excellent
20	Profuse secretion of colostrum starting during third month of pregnancy	33 hours	50 mg. q. 4 h. for 4 doses	50 mg. q. 4 h. for 3 doses	350 mg.	Lactation profuse at onset of medication and remained profuse up to eighth day post partum when 50 mg. of methyl testosterone was given t.i.d. Flow after that diminished. Never any pain, but secretion persisted for 16 days post partum	Poor
21	Marked congestion and pain after previous delivery	38 hours	50 mg. q. 3 h. for 2 doses	30 mg. q. 3 h. for 5 doses	250 mg.	Seant congestion and secretion during treatment. Never any pain. Complete relief 36 hours after last dosage	Good
22	Marked congestion and pain after previous delivery	32 hours	50 mg. q. 3 h. for 2 doses	30 mg. q. 3 h. for 3 doses	190 mg.	Seant congestion during first day of treatment. Never any secretion or pain	Excellent
23	Marked congestion and pain after previous delivery	39 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Seant secretion, and congestion for 24 hours after last dosage. Never any pain	Good
24	Primipara	30 hours	50 mg. q. 4 h. for 4 doses	50 mg. b.i.d.	300 mg.	Moderate secretion, congestion, and discomfort for 36 hours after last dosage	Good
25	Moderate congestion and pain after previous delivery	26 hours	30 mg. q. 3 h. for 5 doses	20 mg. q. 3 h. for 5 doses	250 mg.	Moderate secretion, congestion, and discomfort for 48 hours after last dosage	Fair

Of the 25 patients treated with methyl testosterone, 10 were graded

TABLE II. RESULTS

RATING	NO. OF CASES
Excellent	10
Very good	10
Fair	3
Poor	2

as "excellent," since in these there was no secretion at all, and neither engorgement nor tenderness of the breasts at any time.

Ten cases were graded "very good" since there was mild engorgement, tenderness, and secretion of colostrum only, for twelve to twenty-four hours after the administration of the drug. Three cases were called "fair" since there was moderate secretion of milk with engorgement and tenderness of the breasts during the course of medication or lasting as long as two days after administration of the last dosage. Two cases were called "poor" but in the first of these (Case 12), the medication was not started until seventy-two hours after delivery and at that time the breasts were already engorged, painful, and actively secreting. Here, too, the complete dosage was not given as the result of an oversight and the patient's breasts remained painful, engorged, and actively secreting for one week. The other case (Case 20) rated as "poor" was an unusual one. She was a 22-year-old gravida ii, para ii, whose baby died a few hours after birth. Her ante-partum course was one of severe toxemia and hypertension. With her first pregnancy in 1939 she had profuse colostrum from the third month on. She nursed for eight months with heavy secretion at all times and required seven weeks to dry up breasts on weaning. With her present pregnancy she also had the same leakage of colostrum from the third month on.

Dosage was started thirty-three hours after delivery, at which time her breasts were already congested, somewhat tender, and with profuse secretion of milk. Three hundred and fifty milligrams of methyl testosterone were given over a period of forty-eight hours. The congestion and tenderness disappeared by the time the treatment was stopped but secretion persisted heavily for seven days. On the eighth post-partum day, another 150 mg. were given with resultant cessation of all lactation within forty-eight hours. Since the prime purpose of the medication was to suppress lactation, we overlook the relief from discomfort in this case and rate her as a "poor" result.

As a contrast to these above "poor results" several of the more interesting of the "successful" cases are worthy of detailed description.

CASE 1.—Patient was a 30-year-old gravida ii, para ii who developed severe congestion and a right-sided breast abscess after delivery two years ago. In the present instance her baby was taken off breast four days after delivery. At that time her breasts were congested, tender, and actively secreting. She was given methyl testosterone, 50 mg. every three hours for 4 doses on the fourth post-partum day and 30 mg. t.i.d. on the fifth day. Total dosage was 290 mg. The breasts remained congested and secreting for twenty-four hours after cessation of medication and then rapidly became decongested and nontender. Forty-eight hours after treatment she was entirely comfortable, and there was no longer any secretion of milk.

CASE 3.—Patient was a 29-year-old gravida ii, para ii whose first pregnancy terminated in a stillbirth. The usual methods to suppress lactation were instituted at that time but her breasts remained swollen, tender, and actively secreting for three weeks after delivery. This finally resulted in a leftsided breast abscess and two episodes of incision and drainage. Her second pregnancy, despite a negative Wassermann, also terminated in the delivery of a macerated, stillborn infant. Starting thirty hours after delivery, she was given 30 mg. of methyl testosterone every three hours for 5 doses and then on the following day, 20 mg. every three hours for 5 doses. Total dosage was 250 mg. Her breasts remained soft, nontender and nonsecreting, throughout the entire puerperium.

CASE 4.—This case is also worthy of description. She was a 34-year-old gravida iii, para ii delivered on the private service of Sloane Hospital. After her previous delivery, two years ago, she nursed her baby for one week and then attempted to wean it because of inverted nipples. Lactorrhea developed and persisted for almost a whole year despite several courses of $MgSO_4$ administration with restriction of fluids, binders, etc. During this period of time there were several flare-ups of bilateral mastitis. With the latest pregnancy, excessive lactorrhea developed on the third post-partum day and again, despite epsom salts, tight breastbinders and restricted fluids, the breasts remained tender, congested, and over-actively secreting. Since she again had inverted nipples, her infant was not allowed to nurse. The secretion of milk was so active that fresh towels were required every two or three hours to absorb the overflow. Methyl testosterone was started on the twelfth post-partum day. Forty milligrams were given every three hours for four doses and on the following day 30 mg. every three hours for 5 doses. The total dosage, given over a period of thirty-six hours, was 300 mg. The breasts were distinctly softer by the evening of the second day of treatment and the secretion of milk was reduced by 50 per cent. Forty-eight hours after the cessation of treatment, the breasts were found to be only slightly congested and the flow of milk reduced by 75 per cent. She was discharged that evening, and we were later informed by her private physician that lactation had ceased completely on the fourth day after cessation of treatment.

CASE 13.—Patient was a 37-year-old gravida ii, para ii whose first baby was stillborn. She was treated at that time with epsom salts, breastbinders, and restricted fluids. However, her breasts remained congested, tender, and actively secreting for three weeks after delivery. Following her latest delivery, methyl testosterone was started thirty-six hours post partum. The dosage given was 50 mg. every four hours for 4 doses for a total of 200 mg. There was very mild congestion for twenty-four hours after cessation of treatment but at no time was there any secretion of colostrum or milk and absolutely no discomfort.

DOSAGE

The average case received 30 mg. of methyl testosterone every three hours for 5 doses, starting thirty-six hours after delivery and continuing the following day with 20 mg. every three hours for 5 doses; total $150 + 100 = 250$ mg.

Some patients were given 50 mg. t.i.d. for 3 doses, starting thirty-six hours after delivery and then 30 mg. t.i.d. on the next day, making 290 mg.

Other patients did well on 50 mg. every three hours for 4 doses, making 200 mg.

CONTROL

Eight control cases were run. These patients received no medication at all. They all developed congestion, secretion, and discomfort, lasting from three to seven days post partum and requiring breastbinders, ice caps, restriction of fluids, codeine, and other sedatives.

CONCLUSIONS

Methyl testosterone, in adequate dosage and given at the proper time, is of definite value in the post-partum inhibition of lactation. It brings about "drying-up" of the breasts with a minimal amount of discomfort to the patient since its oral administration removes the necessity for hypodermic injection.

The optimal dosage is about 250 to 300 mg. in divided doses over a period of thirty-six hours and starting about thirty-six hours after delivery. It may also be administered after the actual onset of secretion with beneficial results.

There were no associated symptoms of intolerance.

None of the patients treated required purging with epsom salts, tight breastbinders, icecaps, sedatives, or the limitation of fluids, milk, butter, or cream.

All patients, even those rated "poor," agreed that they were more comfortable with this form of treatment than during their earlier pregnancies when the "old-fashioned way" of drying up the breasts by use of Epsom salts, breastbinders, icecaps, and restriction of fluids, was used.

The puerperium was otherwise unaffected by the medication and on follow-up visit in the post-partum clinic the menstrual periods of these women were found to have returned "normally."

Endometrial studies on these cases are now being carried on to determine whether methyl testosterone has any effect on the subsequent menstrual cycles.

The author wishes to thank Professor Benjamin P. Watson, Director of the Sloane Hospital for Women, for his constructive criticism and for permission to carry on this work.

Thanks are also extended to the nursing staff of Sloane Hospital for their cooperation and skillful observations of the patients.

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CAFFEINE AS AN AID TO SODIUM PENTOBARBITAL ANALGESIA IN LABOR

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THE search for the ideal drug or combination of drugs for obstetric analgesia and amnesia has been long and arduous. It has been stated that the proper drugs have not been discovered. In recent years however, the barbiturates have given promise of fulfilling the varied requirements for ideal effect. Sodium pentobarbital in particular seems to be the most likely of the many preparations that have been tried. Nevertheless, and notwithstanding many clinical studies which emphasize the favorable results attained by the use of sodium pentobarbital alone or in combination, there still remain certain objectionable features, viz.: the confusion, restlessness, and maniacal states which this drug may cause. In the most recent review of the progress of the barbiturates in obstetric analgesia, Hellman¹ points out that "the chief objection to all analgesia technics has been, and remains today, the excitatory action of the drugs. . . . The future development of obstetric analgesia seems to depend on the discovery of compounds whose action is less excitant and whose effects are more controllable."

Since experiments with new and different barbiturates have not been promising, another combination of drugs was sought. At the suggestion of the late Dr. Bernard Fantus, to whom the objectionable features of sodium pentobarbital analgesia were outlined, we decided to add caffeine, a mild cerebral stimulant, to the drug. Thus the delirium of the mother which may be due to a cutting-off of the control of the voluntary cerebral impulses might be counteracted by the mild cerebral stimulation of caffeine. The purpose of this paper is to report the results of these experiments. While the number of cases is not large, it is a well-selected and controlled group and reflects the valuable contributory action of this cerebral stimulant; it also intimates that other, more powerful, cerebral stimulants might be valuable adjuncts. We hope that it will open new vistas into the future progress of obstetric analgesia.

METHOD EMPLOYED

In our series the cases were carefully selected from patients having normal labor. The medication was given only to women who had cephalic presentations and who had no complications of toxemia, hypertension, or other medical disease. It was not given to elderly multiparas who had had many and easy deliveries. The analgesia was not administered until the patient was definitely in labor with a 3 to 4 cm. dilatation of the cervix. The initial dose of sodium pentobarbital was 7½ gr.; and additional 3 gr. were given in four to five hours, or whenever the effect, by observation, was wearing off. The largest dose given was 13½ gr.; most patients (89 per cent) received a dosage of 7½ gr. Caffeine citrate in doses of 5 gr. was also administered orally together

with the sodium pentobarbital and was repeated every hour or two in accordance with the excitability of the patient. Occasionally it was given subcutaneously during the second stage of labor when a more immediate action was required. The largest dose given was 35 gr.; the average was 12.6 gr.

In this study a total of 332 patients were observed. They were divided into three groups, as follows: one series of 146 patients were observed in consecutive admission to the normal labor ward who received no medication at all; 60 patients were placed on the control series receiving only the prescribed dosage of sodium pentobarbital, but no caffeine; the final group of 116 patients received both the sodium pentobarbital and caffeine. Table I illustrates their average age, percentage of primigravidas in each group, and average parity of multiparas in each group.

TABLE I

	NO. OF PATIENTS	AVERAGE AGE	% OF PRIMIPARAS	AVER. PARITY OF MULTIPARAS
No medication	146	23½	50	3.5
Sodium pentobarbital	60	22½	50	2.66
Sodium pentobarbital and caffeine	116	22	69	2.63

A special nurse was in constant attendance throughout the course of labor after administration of the drug. Occasionally, the labor would last longer than a twenty-four-hour period. The conduct of such a case was then turned over to the special regime followed at the Cook County Hospital for prolonged labor. However, these cases were not dropped from our series. The longest labor was 57½ hours. There was no deviation in management when the patient was ready for delivery. Supplemental anesthesia was given when needed. Spontaneous delivery was allowed to occur if possible; low forceps was the only operation necessary to deliver patients on sodium pentobarbital medication. The infant was cared for in the usual manner. After delivery sleep usually ensued quickly, although occasionally, a patient would require additional close watching for an hour or two. The following day she would be questioned regarding amnesia and analgesia.

RESULTS

In any discussion of the effects of an obstetric analgesic and amnesic the following maternal and fetal factors must be considered: changes in blood pressure, pulse, temperature, and respirations, excitability and cooperation (with which, perhaps, the toxicity is closely related), changes in length of labor, operative incidence, blood loss, and post-partum morbidity, the amount of supplemental anesthesia necessary, the amount of post-partum sleep, the degree of amnesia and analgesia, the fetal narcosis and mortality, and any evidence of delayed effects on the infant.

As far as blood pressure, pulse, temperature, or respirations were concerned, no unusual or characteristic variations were noted during the course of this study. The absence of any rise in blood pressure is consistent with the findings of Ross² who used the drug therapeutically in the late toxemias of pregnancy. The absence of marked respiratory

depression may be due to the effect of the caffeine counteracting this property of barbiturate medication and the possibility of sudden respiratory collapse or atelectasis as discussed by Cheatham,³ Sheldon,⁴ and Willeox.⁵

The patient's excitability and cooperation were judged by one of two nurses in constant attendance who were exclusively employed on all these cases throughout our study. Cooperation was defined as the ability of the patient to answer to, and to perform, spoken commands by the attending doctor or nurse. A comparison of the results obtained with and without the use of caffeine may be obtained from Table II. When these two groups are compared with each other (not with the total, as recorded), a much higher incidence (18 per cent more) of excellent cooperation and lower incidence of only fair (40 per cent less) and poor (17 per cent less) cooperation is obtained from patients who received caffeine. It is hoped that the use of caffeine and other cerebral stimulants in combination with sodium pentobarbital in a larger series of cases and by other observers will serve to point out, even more markedly, its clinical effect in the allayment of excitability and increase in cooperation of the patient.

After a statistical analysis of the length of the various stages and also of the total length of labor (Table II), the only significant difference noted was the shorter labor of the multiparas receiving no medication. No completely adequate explanation is offered for this occurrence other

TABLE II. COMPARISON OF MATERNAL AND FETAL FACTORS

	SODIUM PENTOBARBITAL		SODIUM PENTO- BARBITAL WITH CAFFEINE		NO MEDICATION	
	NO. OF CASES	% OF CASES	NO. OF CASES	% OF CASES	NO. OF CASES	% OF CASES
Cooperation:						
Excellent	32	53.3	70	63.0		
Good	10	16.7	17	15.4		
Fair	9	15.0	10	9.0		
Poor	9	15.0	14	12.5		
Total length of labor:						
Primiparas		11.54 hr.		11.85 hr.		12.14 hr.
Multiparas		9.94 hr.		9.37 hr.		7.45 hr.
Operation:						
Low forceps	5	8.3	17	15.0	5	3.5
Midforceps	0	0	0	0.0	2	1.5
Morbidity*	2	3.3	3	2.6	†	3.1
Amnesia:						
Excellent	50	83.4	88	78.0		
Fair	9	15.0	22	19.5		
Poor	1	1.6	3	2.5		
Narcosis of in- fant:						
None	46	77.0	95	84.1	143	98.0
Sleepy	11	18.0	13	11.5	1	0.7
Deep	3	5.0	5	4.4	2	1.4

*Corrected morbidity.

†Based on morbidity for the entire year (1940) for the normal labor ward (3,535 patients).

than the fact that these patients had a much higher average parity (Table I), resulting, possibly, in easier labors.

In accordance with Galloway and Smith⁶ and Gruber,⁷ we noted an increase in the operative incidence. However, the low forceps operation was the only interference necessary in all the patients receiving medication. Since the operation of "prophylactic forceps" is not practiced as a routine procedure on all primiparous patients at the Cook County Hospital, the increased incidence of low forceps operations on those women receiving sodium pentobarbital with and without caffeine can be more truly appreciated. We can find no reason to explain this increased incidence in patients receiving caffeine over those who did not receive this drug. The relatively greater number of low forceps operations were satisfactorily performed under local and block anesthetic methods, and there was no material increase in the amount of supplemental inhalation anesthesia necessary in patients receiving sodium pentobarbital medication. No appreciable increase or decrease in the amount of blood loss was noted in any of the comparative series. In spite of the increased operative incidence in all patients given the barbiturate medication, the post-partum morbidity remained constant (Table II).

After delivery the patients were placed in bed, restrained with a sheet across the chest and watched for a short period of time until sleep ensued. Only in one or two instances did a period of excitement last for an hour or two after delivery. The post-partum sleep usually lasted from eight to twelve hours. The following day the patients were questioned in regard to amnesia and analgesia. The results are recorded in Table II. It should be remembered that amnesia is entirely a subjective symptom. The percentage of those patients receiving excellent amnesia was only slightly higher among those not receiving caffeine (83.4 per cent) than among those who did receive this drug (78 per cent). This is not surprising in view of the fact that caffeine is a cerebral stimulant.

A comparison of the fetal narcosis reveals that 85 per cent of the babies delivered of mothers who also received caffeine had no narcosis, while 77 per cent of the babies from mothers who had no caffeine had no narcosis. While this difference is not too striking, we feel that it is a definite indication of a step toward reducing fetal narcosis in obstetric analgesia. The exact mechanism of this aid is not completely understood. Perhaps the caffeine likewise stimulates the fetal respiratory center, as well as the maternal cerebral centers. None of the babies in any of our comparative series died and none showed any delayed effects of the drugs at the time the mother was sent home from the hospital. The most recent articles by Henderson and associates⁸ and by McCormick⁹ tend to show that there is a high degree of general safety and security with well-handled analgesics. They claim that when properly supervised and in the hands of those familiar with their use, analgesics per se do not increase the incidence of asphyxia. McCormick⁹ also states that "by eliminating the 'physiologic weight loss' (which, he claims, is a manifestation of birth shock) and enhancing the fetal and neonatal welfare, wisely used obstetric analgesia is no longer a privilege but a prerequisite of better obstetrics."

While the results of this study are only indicative, still we feel that, clinically, it is a step in the right direction and warrants further experimentation with larger doses and more powerful cerebral stimulants. The use of eoramine and other drugs is suggested.

SUMMARY AND CONCLUSIONS

A comparative study of the effect of caffeine upon sodium pentobarbital analgesia in labor has been made using two groups of patients as controls. One control group received no medication at all; the other received sodium pentobarbital, but no caffeine.

1. Parturient women given sodium pentobarbital with caffeine manifest little, if any, decrease in respiratory rate. The caffeine may counteract the respiratory depression of the barbiturate medication.

2. The addition of caffeine to sodium pentobarbital medication increases the cooperation and lessens the excitability of the parturient patient.

3. Sodium pentobarbital, with or without caffeine, increases the length of labor in multiparas a moderate amount, but these results are indeterminate.

4. No operative procedure other than low forceps was necessary to deliver any patient receiving sodium pentobarbital. However, a larger percentage of those who received caffeine required the low forceps delivery than those who did not receive this drug.

5. In spite of the fact that the operative incidence was increased in all patients receiving sodium pentobarbital medication, the post-partum morbidity was not increased. None of our patients died.

6. Although caffeine stimulates the cerebrum, its addition to sodium pentobarbital caused only slight decrease in the number of patients obtaining excellent post-partum amnesia.

7. A somewhat higher percentage of infants delivered of mothers who received caffeine with the sodium pentobarbital medication showed no narcosis. The exact mechanism of this process is not completely understood; it is possible that the caffeine may stimulate the fetal respiratory center.

8. Clinically we feel that the addition of caffeine constitutes a step in the right direction toward better obstetric analgesia and warrants further work with other drugs.

We wish to extend our sincere appreciation to Dr. Robert B. Lewy and to Miss Elizabeth M. Adles of the Department of Therapeutics for their splendid cooperation, helpful suggestions, and constructive criticism throughout the course of this study. Our thanks are also tendered to Miss Elaine Redding and Miss Helen Watson, our two nurses, for their constant and courteous service.

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BRENNER TUMOR OF THE OVARY ASSOCIATED WITH UTERINE BLEEDING

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THIS report of a Brenner tumor of the ovary is of unusual interest because it occurred in a patient 77 years of age and was associated with symptoms usually ascribed to tumors having an estrogenic endocrinal function, viz., vaginal bleeding and hyperplastic proliferative endometrium.

CASE REPORT

Mrs. F. S., aged 77 years, white, widow, was admitted to hospital on Oct. 3, 1940, with history of recurrent painless vaginal bleeding which occurred for the first time on Dec. 17, 1938, and persisted for three days. There was recurrence of the bleeding nine days later for three days. From January, 1939, to June, 1940, she bled only twice, each time the bleeding lasting one day. The last bleeding occurred Sept. 4, 1940. With the onset of the vaginal bleeding, a definite increase in size of both breasts was noted. Just prior to hospital admission, an endometrial biopsy was obtained, which revealed hyperplastic endometrial glands similar to those seen in hyperactive or persistent proliferative endometrium.

Menarche began at the age of twelve years and the interval of menstruation was twenty-one days with flow, which was always profuse, lasting four days. There was mild dysmenorrhea the first and last days of the flow. Menopause occurred at age 48 and was not accompanied by any unusual symptoms.

Pertinent findings in the physical examination were: mild generalized arteriosclerosis with moderate hypertension and nontoxic adenoma of the right lobe of the thyroid gland. Upon vaginal examination, rugae were present; the vagina was moist and spacious without tears or relaxations; the cervix was normal in size and appearance; the uterus was anterior, smooth, and of normal size for a menstruating woman. Posterior to the uterus, there was a cystic, fixed mass arising from the region of the left ovary. This was approximately 8 cm. in diameter.

At operation on Oct. 4, 1940, a dilatation and curettage were performed, with recovery of a small amount of endometrial tissue. The uterus was smooth, soft and approximately the size of a five to six weeks' pregnancy. The right ovary was 1 by 0.5 by 0.5 cm. and was entirely sclerotic. There were no visible Graafian follicles. Arising from the left ovary and dropping into the cul-de-sac posteriorly, there was a cystic tumor 8 cm. in diameter with a solid area in its wall. Left oophorectomy was performed.

Pathologic Findings.—Specimen (office endometrial biopsy) consisted of a small amount of curetted tissue in narrow strips.

Microscopic Description: Microscopic sections of the tissue revealed endometrium. The surface epithelium was high columnar in type with

nuclei situated at the bases of the cells. The nuclei were slightly hyperchromatic. The glands were simple tubular in type with high columnar epithelium and with nuclei situated at the bases of the cells, for the most part. A few of the glands had atrophic epithelium and were mildly cystic. The cytogenic stroma contained fairly large cells with hyperchromatic nuclei and was only moderately compact. The general appearance was that of endometrium at the eighth to tenth day of a normal twenty-eight-day menstrual cycle.



Fig. 1.—Photomicrograph of biopsy of endometrium revealing glands and stroma in proliferative phase of the menstrual cycle. (H. & E. stain, $\times 100$.)



Fig. 2.—Photograph of gross specimen. Multilocular pseudomucinous cystadenoma with Brenner tumor in wall of cyst. The Brenner tumor is seen as the solid white area in the cyst wall.

Microscopic Diagnosis: Slight hyperplastic, persistent proliferative endometrium.

Tissue Removed at Operation in Hospital (Oct. 4, 1940).—Gross Description: Specimen consisted of a minute amount of uterine curettings

and a cystic tumor of the left ovary. The uterine curettings presented no special characteristics. The specimen of the cystic tumor was nearly spherical in shape and measured 12 by 8 by 8 cm. The outer wall was smooth. It was white to blue in color and the vessels were prominently

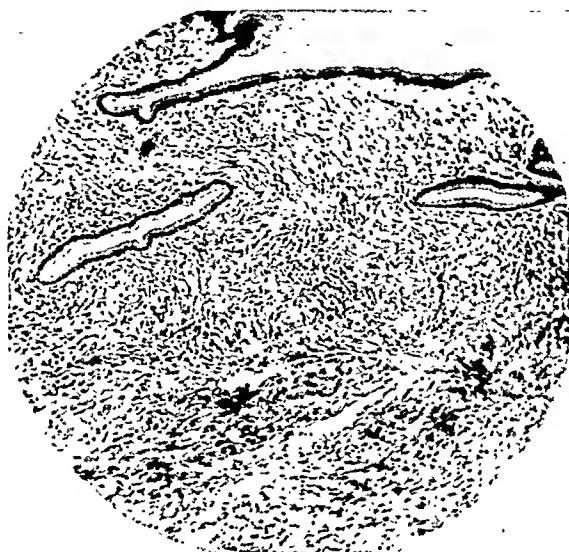


Fig. 3.—Photomicrograph of wall of pseudomucinous cyst revealing mucus-producing epithelium and glands supported by fibrous stroma. (H. & E. stain, $\times 100$.)



Fig. 4.—Photomicrograph from solid area of cyst wall revealing typical Brenner tumor structure, consisting of interlacing growth of dense fibrous connective tissue and islands of epithelium, the so-called Walthard's rests. (H. & E., $\times 100$.)

displayed on its surface. The contents were colorless, clear, thin, slightly mucinous fluid. Upon section the cyst was found to be multilocular, the largest locule being 8 cm. in diameter. There were four other locules which were definite and measured from 2 to 5 cm. in diameter. There were no papillary projections upon the internal wall, the wall being

smooth and white to pink in color. Vascular markings were also prominent. Growing from the inner wall of the larger locule, a large, solid, very firm, slightly rounded tumor mass, which measured 6 by 5.5 by 2.5 cm., was found. The color of the mass was white to yellow. The cut surface was coarsely fasciculated by interlacing bundles of tissue.

Microscopic Description: Microscopic sections of the cyst wall stained by hematoxylin-eosin revealed it to be lined by simple columnar epithelium. Nuclei were basal. The borders of the epithelial cells were faintly stained or clear, representing mucus content. The supporting tissue of the cyst was of loose fibrous connective tissue type. Microscopic sections taken from the solid tumor stained by hematoxylin-eosin revealed dense interlacing bundles of mature fibrous connective tissue which contained nests of epithelial cells. The cytoplasm of the epithelial cells was fairly abundant and pale staining. The nuclei were pale or slightly vesicular. The epithelial cell masses were sharply circumscribed from the surrounding connective tissue and had the general appearance of Walthard inclusions as found normally about the Fallopian tube and ovary. Occasionally, there were small cystic cavities in the centers of the epithelial masses. There were no mitotic figures in any part of the tumor or the cyst wall.

Microscopic Diagnosis: Multilocular, nonpapillary, pseudomucinous cystadenoma with Brenner tumor in wall of cyst (left ovary).

DISCUSSION

• Brenner tumors fall into two well-defined groups. They are either solid tumors resembling fibromas, or pseudomucinous cystomas in the walls of which the Brenner tumor stands out as a solid nodule. There are great variations in the size of the tumor. Some are of microscopic size, while others may become very large even when not associated with cystomas. The gross appearance of the solid tumors is quite similar to that of a fibroma, although there is frequently a yellowish tint to the cut surface. There is only slight tendency to necrosis and hemorrhage but cystic degeneration is more common, in the solid variety. No definite capsule exists, although the surrounding ovarian stroma is more or less compressed.

Microscopically, there are scattered cell groups lying in a superabundant fibrous stroma. The cell groups are compact and the cells may be polyhedral, cubical, cylindrical, rarely ciliated and occasionally stratified. Small cysts are frequently formed from degeneration of the compact cell masses. Glycogen is present in the cells. Fat is absent. The stroma, which comprises the bulk of the tumor, is composed of spindle cells with collagen fibrils and is frequently hyalinized.

There are three theories as to the histogenesis of the tumor. Robert Meyer¹ believed that the tumor arose from islands of indifferent cells in the ovary first fully described by Walthard² and since called Walthard inclusions. These are found in the superficial portion of the ovary or, frequently, in the uterine tubes and uterine ligaments, especially in the newborn and young child, but also in the adult. They consist of nests of cells resembling squamous epithelium or transitional, often showing cystic cavitation, or actually converted into tiny cysts, or the inclusions may take the form of glandlike spaces lined by columnar or ciliated epithelium, with at times definite mucus formation. Schiller's³ theory was postulated on a dislocation of cells from a primitive urogenital con-

nection. A third theory considers that the tumors are one-sided developments of teratomas. This is based on the occasional association with pseudomucinous cystomas, which also are regarded as one-sided developments of teratomas by certain investigators.

Clinically the tumor is benign and slowly growing. Sixty per cent occur after the menopause. In the literature the oldest patient reported with a Brenner tumor was aged 71, and the youngest aged 25 (Novak⁴). In the majority of reports the tumors were an incidental finding to other pathologic changes of the female generative organs.

Practically all observers who have written about the Brenner tumor say that there is no endocrine effect produced by the tumor.⁵⁻⁷ Novak⁴ reported one case of postmenopausal bleeding associated with a Brenner tumor. The endometrium was not studied, and he does not think the bleeding was related to the presence of the tumor. Postmenopausal bleeding is said to have occurred in a number of other cases in which the endometrium was not studied. Novak further stated that in spite of this, there is no reason to think that the bleeding was due to any direct endocrine effect upon the uterus. Usually, the uterus in elderly women with Brenner tumor has been described as senile and atrophic.

Fauvet⁸ reported 4 cases of Brenner tumor, 3 of which presented postmenopausal bleeding. Two of the 3 cases exhibited polypoid endometrium. He concluded that there is neither clinical nor microscopic evidence that the Brenner tumor is the source of hormonal reactivating or rejuvenating substances; however, he thought it may be attributed to extragenital endocrine stimuli, possibly from the adrenal cortex.

Schiffman⁹ reported endometrial hyperplasia and uterine bleeding in association with a Brenner tumor.

TeLinde¹⁰ cited a case of Brenner tumor in a woman aged 62 who exhibited profuse recurrent postmenopausal bleeding, diabetes and hypertrichosis. She had a tumor replacing the right ovary and adenocarcinoma of the endometrium.

In a later communication, TeLinde¹¹ listed the Brenner tumor as one of a group of tumors associated with postmenopausal bleeding.

In any analysis of postmenopausal bleeding, it will be found that pseudomucinous cystomas have been found to be associated in a small percentage of cases with hyperplasia of the endometrium. Taylor¹² in a recent review believed that endometrial hyperplasia associated with a pseudomucinous cystoma may be the result of a general hyperemia in the pelvis from the presence of the tumor or possibly also the result of substances elaborated by the cysts or by activated ovarian cells in the walls of the cysts. Therefore, it would not be unusual that the Brenner tumor possessed the ability to initiate uterine bleeding, since some are associated with pseudomucinous cystomas.

Our case exhibited effects usually attributed to the estrogens, such as vaginal bleeding, breast development, a good-sized uterus, normally appearing cervix, spacious vagina, and rugae with a hyperplastic proliferative type of endometrium. Thus, more evidence than vaginal bleeding alone is offered in support of the theory that the tumor was hormonally active. Vaginal bleeding alone without supporting evidence should probably be taken only as a sign of pelvic congestion. Estrogens administered to ovariectomized animals and women will produce the changes which were observed in our patient.¹³

Postmenopausal bleeding in the absence of uterine pathologic changes must be considered as a form of menstruation. It is now accepted that the menses are probably degenerative but depend upon endocrine factors whose activity has preceded the onset of bleeding. These factors apparently need not include corpus luteum hormone (as in the anovulatory cycles), therefore, estrogens alone may be sufficient to explain the essential mechanism of menstruation.¹⁴ Assay for estrogens would probably have decided the matter in our case, but unfortunately this was not done.

One theory of origin of the tumor favors the hypothesis that the Brenner tumor may be hormonally active, since it is related to an early undifferentiated phase of genital development. It may be argued that the cells of the tumor may function along female lines in certain cases.

Goodall¹⁵ says that embryonic rests in the ovary may remain dormant for all time or may be awakened into activity by any one of many stimuli at any age. Many, if not all, of these rests are aroused to proliferation as a result of nutritional changes. These changes may be primary vascular or neurotrophic. The nutritional influence may operate by stimulation of the normal ovarian function to abnormal development or by stimulation of the abnormal embryonic rests in the ovary to pathologic activity and sometimes to unbridled aberrant growth.

CONCLUSION

Estrogenic hormone production is not definitely excluded as a biologic function of a Brenner tumor, since in this case, the tumor occurred in a 77-year-old woman and many of the anatomic and physiologic changes usually associated with the presence of estrogens were found.

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THE USE OF QUICK FREEZING METHODS IN GYNECOLOGIC PRACTICE

A PRELIMINARY REPORT

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LIKE thermotherapy, cryotherapy, or the treatment with cold, may be divided into two types: in one cold is applied in such a way that no damage is inflicted on the cellular structures; in the other the integrity of such structures is destroyed. Cold compresses and ice bags are extensively employed for the relief of pain in acute and chronic inflammatory processes, and satisfactory local anesthesia has been obtained through the use of the ethyl chloride spray. Solid carbon dioxide and liquid oxygen have been used for the destruction of pathologic growth in various fields of medicine, including gynecology.

Pusey¹ published the first report in 1907, on the successful treatment of cutaneous disorders with solid carbon dioxide. In 1927 and 1928 Kroh² reported a series of more than 900 cases of various cutaneous disorders, including furuncles and carbuncles, in which treatment with solid carbon dioxide was used. He expressed the belief that the results of such treatment were better than those obtained with radium therapy, because the scars stayed pliable, were not contractile, and displayed no tendency to keloid formation.

In 1930 Lortat-Jacobs and Solente³ reported their results from the use of the cryocautere, an instrument consisting of a container and a rodlike applicator filled with a mixture of solid carbon dioxide and acetone. On the basis of biopsies they concluded that the results from using this instrument in the treatment of chronic endocervicitis and erosions of the cervix were superior to those obtained with the electric cautery, since after treatment there was complete regeneration of the mucous lining without contractile scars. The chief objections to their instrument are the size of the freezing mixture container, which reduces visibility and the limited time of application of cold.

More recently, Weitzner⁴ reported excellent results from the use of solid carbon dioxide in 325 cases of cervical erosions and endocervicitis. From biopsies, which were performed in 111 cases, he discovered that as early as seven days after treatment epithelial proliferation resembling carcinoma was present in 30 per cent of the cases. This observation prompted him to discontinue treatment for one year and to investigate further the changes taking place in the healed lesions of the cervix, which macroscopically appeared smooth and normal. The pseudo-carcinomatous proliferation was present for from three months to two and one-half years before it disappeared. He concluded that these observations substantiated those of Berenblum,⁵ who in 1929 and in 1930 had carried out similar studies and had expressed the opinion that

cryotherapy has no carcinogenic effect and that the proliferation merely represented increased activity of the healing epithelium.

In a paper published in 1939, Smith and Fay⁶ pointed out that there is a critical temperature below which young undifferentiated cells become inactive and undergo degeneration. They discovered that the lowest temperature at which healthy mature cells may be kept intact is about +40° F. These investigators actually employed not slow freezing but only cooling of the tissues, a method which differs essentially from quick freezing, in which the tissues are momentarily exposed to extremely low temperatures.

Notwithstanding the excellent results obtained with quick freezing, this method of treatment has not gained the place it deserves in the medical armamentarium. The explanation for this lies in the nature of the instruments available for the application of cold, for they are satisfactory only for applications to exposed areas. One major objection to using these instruments in body cavities has been the difficulty of removing the applicator once the tissue has been frozen. Consequently, it occurred to me that, if a more practical means of applying cold were devised, cryotherapy might gain the wider place it deserves. With this end in view an apparatus* has been developed which, it is believed, overcomes the disadvantages of its predecessors. The basic operating principle is the same as that of the electric refrigerator as is evident from Fig. 1.

APPARATUS

The refrigerant medium used in the apparatus is Freon gas, or dichlorodifluoromethane (CF_2Cl_2). This gas was chosen because it is nonexplosive, noninflammable, and nonpoisonous. By circulating this gas under a pressure of 100 pounds (45.5 kg.) an even temperature of -40° F. can be maintained. Dr. Fay and coworkers,⁷ who are at present experimenting with this apparatus, have obtained temperatures of -6° to -8° F. within the tissues at the time the frosting started on the surface, determined by means of a thermocouple. This, in their opinion, is well within the range of effectual therapy.

One of the most important advantages of the apparatus is its defrosting device, which facilitates the removal of the applicator from the frozen tissue. Simply by short-circuiting and returning the expanded and heated gas, under low pressure, into the expansion chamber, the applicator is defrosted and easily removed.

The instrument is equipped with an electric sterilizer and an automatic stop clock, which facilitates the administration of treatment for a predetermined length of time. The three permanently attached applicators are designed for gynecologic therapy; two, of different sizes, are intended for straight insertion into the cervical canal and the third for flat application to the cervix.

CLINICAL OBSERVATIONS

We have used this instrument in 60 cases in which there was a diagnosis of chronic endocervicitis, cervical erosion or cervical polyp, singly or in combination. Data for these cases are given in Table I.

*Made by Peerless of America, Marian, Ind.

Twenty-three cases were treated for erosion of the cervix, 18 for endocervicitis, 13 for erosion associated with endocervicitis, 2 for cervical polyp, 3 for cervical polyp associated with erosion, and 1 for multiple cervical polyps associated with erosion and endocervicitis. The average number of treatments was 1.58 and the average time for the cervical

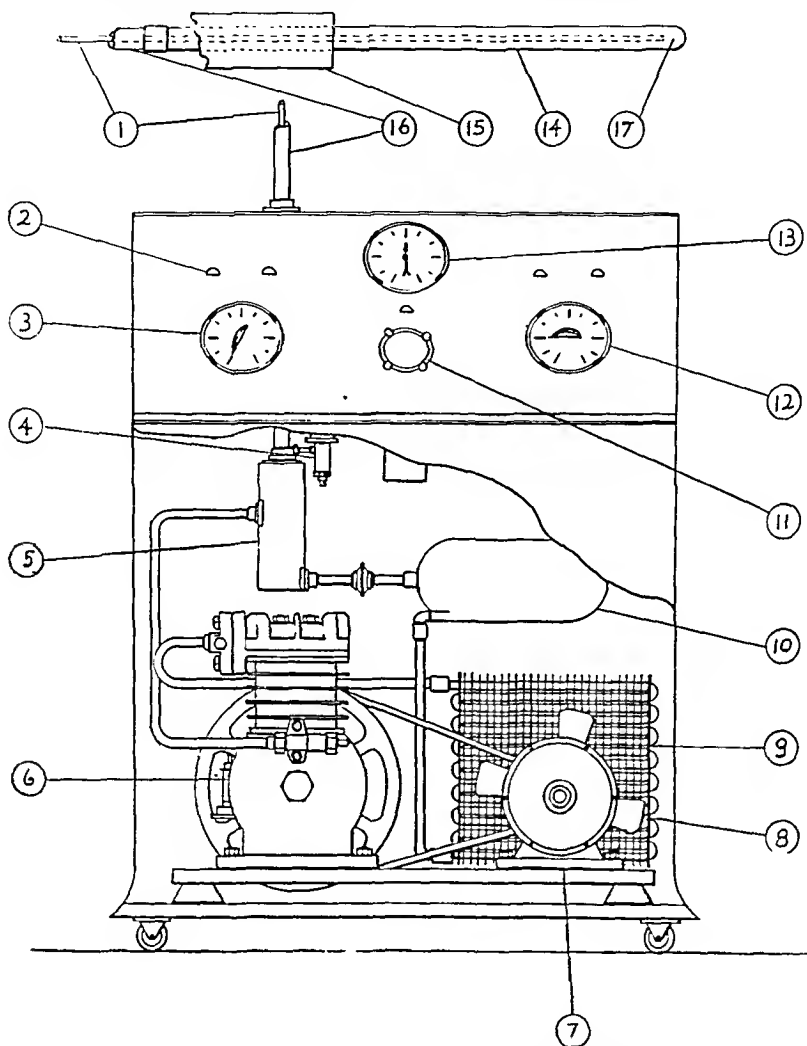


Fig. 1.—1, Liquid line; 2, control indicator lights; 3, switch and time control for length of freezing; 4, thermostatic control; 5, distribution chamber; 6, pump and compressor; 7, motor; 8, fan for condensor; 9, condensor; 10, receiver tank; 11, sterilizer for applicators; 12, defrosting switch; 13, sterilizer switch; 14, applicator (straight); 15, rubber insulator; 16, suction tube; 17, expansion chamber.

By turning switch (3), motor (7) is started, pumping refrigerant from receiver tank (10) into distribution chamber (5) with thermostatic control (4) and through liquid line (1) into expansion chamber (17) in applicator (14), then returning refrigerant through suction tube (16) into compressor (6) and into condensor (9), cooled by fan (8) and back into receiver tank (10), thus completing a full cycle. Defrosting switch (12) returns heated refrigerant into expansion chamber (17). Switch (12) starts sterilizer (11). Control lights (2) are flashed by turning switches (3, 12, 13) indicating operation of freezing, defrosting and sterilizing, respectively.

For the sake of simplicity only one applicator is shown. The applicators are insulated with hard rubber tubings (15).

The machine is mounted on rubber wheels, weighs 165 pounds, and has a forward sloping instrument panel. Base measures 43 by 43 cm., height in front 69 cm., in rear 80 cm. The flat applicator is 20 cm. long. The circular surface for freezing has a diameter of 2 cm. The straight applicators are 25 cm. long, with a width of 8 and 5 mm., respectively, and have removable hard rubber insulators.

TABLE I. RECORD OF CASES

CASE	AGE	GRAV.	DIAGNOSIS	DATE	TIME OF APPLI- CATION MIN.	TYPE OF APPLICA- TION	LAST EXAM.	RESULT
1	31	0	Endocervicitis	12/ 6/39	3	Intracerv. 6 cm.	3/ 7/40	Healed
				2/ 4/40	6	Intracerv. 6 cm.		
2	25	i	Endocervicitis	1/23/40	6	Intracerv. 6 cm.	2/29/40	Healed
3	39	0	Endocervicitis	1/24/40	3	Intracerv. 6 cm.	4/ 5/40	Healed
				2/22/40	6	Intracerv. 6 cm.		
4	24	iii	Large erosion	3/15/40	5	Intracerv. 3 cm.	4/30/40	Healed
				4/12/40	5	Intracerv. 3 cm.		
5	23	i	Small erosion	4/12/40	6	Intracerv. 3 cm.	6/ 7/40	Healed
6	22	ii	Small erosion	5/13/40	8	Intracerv. 3 cm.	6/ 7/40	Healed
7	44	i	Papill. erosion	7/ 7/40	6	Intracerv. 6 cm.	11/20/40	Healed
			Multiple polyps	7/ 7/40	6	Flat to cervix		
				7/29/40	10	Intracerv. 6 cm.		
			Endocervicitis	11/14/40	5	Intracerv. 6 cm.		
8	47	ii	Small erosion	8/ 7/40	6	Intracerv. 3 cm.	9/28/40	Healed
			Endocervicitis					
9	26	ii	Large erosion	8/24/40	6	Intracerv. 6 cm.	1/ 5/41	Healed
			Endocervicitis	8/24/40	3	Flat to cervix		
				11/ 2/40	8	Intracerv. 6 cm.		
10	41	i	Endocervicitis	9/19/40	10	Intracerv. 6 cm.	3/29/41	Unchanged
			(Retrover- sion)	11/14/40	3	Intracerv. 6 cm.		
11	29	ii	Papill. erosion	9/19/40	3	Flat to cervix	11/ 8/40	Healed
12	24	ii	Large erosion	9/28/40	7	Intracerv. 6 cm.	2/ 1/41	Healed
			Endocervicitis	10/12/40	10	Intracerv. 6 cm.		
13	25	iii	Large erosion	10/ 5/40	10	Intracerv. 6 cm.	11/ 9/40	Unchanged
			Endocervicitis	10/ 5/40	3	Flat to cervix		
				11/ 2/40	8	Intracerv. 6 cm.		
14	33	ii	Small erosion	10/23/40	10	Intracerv. 3 cm.	12/13/40	Healed
			Large polyp					
15	30	0	Endocervicitis	10/23/40	10	Intracerv. 6 cm.	11/19/40	Healed
16	37	0	Endocervicitis	10/23/40	6	Intracerv. 6 cm.	2/24/41	Healed
				12/23/40	1	Intracerv. 6 cm.		
				1/17/41	1	Intracerv. 6 cm.		
				1/24/41	1	Intracerv. 6 cm.		
17	29	ii	Large erosion	10/26/40	8	Intracerv. 6 cm.	2/ 1/41	Healed
			Endocervicitis	11/23/40	3	Intracerv. 6 cm.		
				11/23/40	4	Flat to cervix		
				12/28/40	2	Intracerv. 6 cm.		
				12/28/40	2	Flat to cervix		
18	33	0	Endocervicitis	10/28/40	2	Intracerv. 6 cm.	5/10/41	Healed
19	22	i	Large erosion	11/ 2/40	5	Flat to cervix	1/29/41	Healed
				11/23/40	3	Flat to cervix		
				12/29/40	3	Flat to cervix		
20	34	0	Small polyp	11/ 2/40	2	Intracerv. 3 cm.	11/24/40	Healed
21	19	0	Small erosion	11/ 2/40	2	Intracerv. 3 cm.	2/ 1/41	Healed
22	50	ii	Large polyp	11/18/40	5	Intracerv. 3 cm.	12/16/40	Healed
				11/18/40	2	Flat to cervix		
23	50	i	Endocervicitis	11/20/40	3	Intracerv. 6 cm.	12/21/40	Healed
				12/ 4/40	2	Intracerv. 6 cm.		
24	46	iv	Small erosion	12/ 2/40	2	Intracerv. 6 cm.	2/ 8/41	Healed
			Endocervicitis					
25	27	0	Endocervicitis	12/10/40	2	Intracerv. 6 cm.	6/27/41	Healed
				1/22/41	1	Intracerv. 6 cm.		
				2/ 7/41	1	Intracerv. 6 cm.		
26	40	0	Small erosion	12/11/40	3	Flat to cervix	2/20/41	Healed
				12/26/40	3	Flat to cervix		
27	25	i	Large erosion	12/13/40	2	Flat to cervix	2/28/41	Healed
			Endocervicitis	1/ 3/41	1	Intracerv. 6 cm.		
				2/ 4/41	2	Intracerv. 6 cm.		

TABLE I—CONT'D

CASE	AGE	GRAV.	DIAGNOSIS	DATE	TIME OF APPLI- CATION MIN.	TYPE OF APPLICA- TION	LAST EXAM.	RESULT
28	43	iii	Endocervicitis	12/13/40	2	Intracerv. 6 cm.	3/24/41	Healed
29	23	ii	Small erosion	12/14/40	3	Intracerv. 6 cm.	5/12/41	Healed
			Endocervicitis	12/14/40	3	Flat to cervix		
				2/ 1/41	3	Intracerv. 6 cm.		
				2/ 1/41	3	Flat to cervix		
				3/26/41	1	Intracerv. 6 cm.		
30	28	0	Endocervicitis	12/17/40	2	Intracerv. 6 cm.	2/ 3/41	Healed
31	25	i	Large erosion	12/24/40	2	Flat to cervix	2/28/41	Healed
				1/10/41	2	Intracerv. 3 cm.		
				1/25/41	1	Intracerv. 3 cm.		
32	65	ii	Papill. erosion	12/28/40	1	Intracerv. 3 cm.		
				12/28/40	1	Flat to cervix		
				1/10/41	1	Intracerv. 3 cm.		
33	26	0	Small erosion	12/30/40	1	Intracerv. 3 cm.	3/24/41	Healed
			Endocervicitis	1/20/41	2	Intracerv. 3 cm.		
				1/27/41	2	Intracerv. 3 cm.		
34	24	i	Large erosion	1/13/41	1	Intracerv. 3 cm.	2/26/41	Healed
				1/13/41	1	Flat to cervix		
				2/13/41	2	Intracerv. 3 cm.		
35	27	i	Endocervicitis	1/14/41	2	Intracerv. 6 cm.	3/ 6/41	Healed
36	28	ii	Large erosion	1/15/41	1	Intracerv. 3 cm.	2/24/41	Healed
				1/15/41	2	Flat to cervix		
37	34	0	Endocervicitis	1/16/41	2	Intracerv. 6 cm.	3/20/41	Healed
38	27	i	Large erosion	1/17/41	1	Flat to cervix	2/21/41	Healed
				1/31/41	1	Flat to cervix		
				2/ 7/41	1	Flat to cervix		
39	26	ii	Endocervicitis	1/20/41	1	Intracerv. 6 cm.	3/ 4/41	Healed
40	35	ii	Large erosion	1/24/41	2	Flat to cervix	3/21/41	Healed
				2/ 7/41	2	Flat to cervix		
				2/21/41	1	Flat to cervix		
41	35	i	Large erosion	1/24/41	1	Flat to cervix	3/28/41	Healed
				2/14/41	1	Flat to cervix		
				3/14/41	1	Flat to cervix		
42	31	i	Endocervicitis	1/25/41	2	Intracerv. 6 cm.	3/26/41	Healed
43	36	ii	Large erosion	1/29/41	2	Flat to cervix	5/14/41	Healed
44	35	0	Small erosion	1/31/41	1	Flat to cervix	3/14/41	Healed
45	49	0	Small erosion	1/31/41	1	Intracerv. 6 cm.	5/14/41	Healed
			Endocervicitis					
46	29	0	Small erosion	2/ 4/41	2	Intracerv. 3 cm.	2/25/41	Healed
			Small polyp					
47	31	ii	Large erosion	2/ 5/41	2	Flat to cervix	3/ 8/41	Healed
48	33	0	Endocervicitis	2/ 6/41	1	Intracerv. 6 cm.	3/16/41	Healed
49	29	0	Large erosion	2/12/41	1	Flat to cervix	5/12/41	Healed
50	32	ii	Small erosion	2/12/41	2	Intracerv. 3 cm.	3/11/41	Healed
			Endocervicitis					
51	19	0	Large erosion	2/14/41	1	Flat to cervix	5/13/41	Healed
52	24	ii	Small erosion	2/17/41	1	Intracerv. 3 cm.	3/26/41	Healed
53	35	ii	Small erosion	2/20/41	4	Intracerv. 3 cm.	3/24/41	Healed
			Large polyp					
54	29	iii	Papill. erosion	2/22/41	2	Intracerv. 3 cm.	7/ 2/41	Healed
55	34	ii	Small erosion	2/28/41	1	Flat to cervix	3/28/41	Healed
56	36	0	Small erosion	3/ 3/41	1	Intracerv. 6 cm.	3/24/41	Healed
			Endocervicitis					
57	31	i	Large erosion	3/22/41	1	Flat to cervix	6/15/41	Healed
58	20	0	Large erosion	5/24/41	1	Flat to cervix	6/17/41	Healed
59	36	iii	Large erosion	5/26/41	1	Endocerv. 6 cm.	6/30/41	Healed
			Endocervicitis	5/26/41	1	Flat to cervix		
60	50	iv	Small erosion	6/10/41	1	Intracerv. 6 cm.	7/10/41	Healed
			Endocervicitis					

lesions to heal was 63.4 days. Only two patients, belonging to the endocervicitis group did not improve, a failure of 3.3 per cent. Patients 18 and 25, who also belonged to the endocervicitis group, were already classified as failures, but when they returned at a later date, the examination revealed the cervical canal healed. As can be seen from Table I, a considerable time may elapse before the beneficial results become apparent. These observations convinced us that the final judgment for success or failure should be postponed until at least six months have elapsed from the first treatment given. Patient 13, diagnosed as large circular erosion and nonspecific endocervicitis, developed after a second treatment of eight minutes, 5 cm. intracervically, fever with pain in the lower abdomen, which subsided after four days. Three days later she was examined at the clinic. The vaginal examination failed to reveal any involvement of the parametria, but the cervical discharge was still as profuse as before. She did not return for further observation and had to be classified as failure. A similar reaction took place in Patients 16

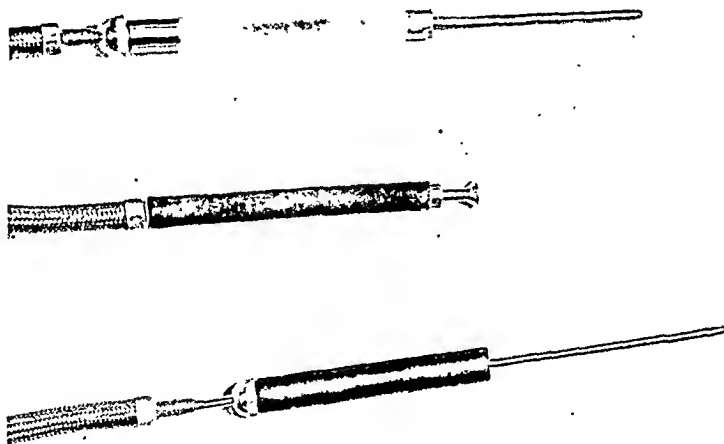


Fig. 2.—Applicators, showing portions of the flexible high pressure metal tubes leading to the distribution chamber.

and 17, in whom the applicator was inserted for more than 3 cm. into the cervical canal and the freezing applied for more than five minutes. Neither developed a cellulitis or a parametrial abscess, and in both patients the cervix cleared up in less than four months. The failure of Patient 10 to respond to the treatments may partly be ascribed to her refusal to have the malposition of her uterus rectified.

In cases of erosions of the cervix, the character of the lesion determines the length of the treatment. Plain superficial erosions may be treated for one to two minutes. Large circular erosions, including those of the papillary type, ectropions, and cervical polyps require from two to ten minutes' treatment. In patients with endocervicitis, where the applicator is introduced into the cervical canal for more than 3 cm., the treatment should not exceed two minutes. From our experience it seems advisable to treat erosions of the cervix not oftener than once every two weeks, and to repeat intracervical applications only once every four weeks. In acute infections of the uterus, the application of quick freezing, even for a very short period, is absolutely contraindicated.

SUMMARY

A new apparatus for quick freezing, the basic operating principle of which is the same as that of the electric refrigerator, has been described. The applicators are especially designed for gynecologic therapy and the apparatus is equipped with a defrosting device, which greatly simplifies their removal from frozen tissue.

Excellent therapeutic results were obtained with this instrument in 60 cases of chronic endocervicitis, cervical erosions and cervical polyps.

I wish to express my grateful appreciation to Dr. Ashley M. Brand for his helpful assistance in developing the quick-freezing therapy, and for supplying me with the data of his patients treated at the Chicago Maternity Center; also to Mr. R. W. Krieger for cooperation in constructing the apparatus.

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25 EAST WASHINGTON STREET

DeMarsh, Q. B., Alt, H. L., Windle, W. F., and Hillis, David S.: The Effect of Depriving the Infant of Its Placental Blood, J. A. M. A. 116: 2568, 1941.

Deprivation of the infant of its placental blood by clamping the umbilical cord immediately after delivery results in significantly lower values for red blood corpuscles and hemoglobin during the first week of life than are encountered when clamping is delayed. In addition there is an increase in the number of reticulocytes in the blood. The placental blood belongs to the infant, and his failure to get this blood is equivalent to submitting him to a rather severe hemorrhage. Failure to receive this placental blood is especially important in prematures. It is estimated that 25 per cent of the infant's total blood volume may be lost by clamping the cord immediately after delivery. The authors condemn the practice of clamping the cord immediately after birth, and incidentally condemn the use of placental blood for transfusion purposes.

WILLIAM BERMAN.

LOCAL ARGYRIA OF UTERUS AND TUBE*

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ARGYRIA, local or general, results from absorption of silver compounds by a mucous membrane or by tissue fluid. The silver may be applied as a soluble salt, an organic compound, or in colloidal form.^{10-12, 17} Metallic silver can be oxidized by body fluids. The resulting silver compounds, probably silver albuminates,^{7, 9, 14} are absorbed. Rodin¹⁵ described a case of argyria of the eyeball in a patient who carried a silver stylet in the lacrimal sac for seventeen years. Warthin¹⁶ found extensive argyria of the inguinal lymph nodes twenty years after the insertion of silver wire for repair of an inguinal hernia.

The danger of argyria, neglected since the abolition of long-standing treatment with pills of silver nitrate, has been stressed again in recent years^{5, 9} due to many cases of argyria following intense local or intravenous treatment with modern silver compounds. Quantitative investigations have proved that the human body may deposit a certain amount of silver in connective tissue before general argyria appears. In intravenous treatment with silver arsphenamine,^{5, 8} the absorption can be estimated quantitatively. Under such conditions a definite relation between the total dosage and the silver content of the skin has been established.

The silver, once deposited, remains unchanged for a lifetime. Reports about the appearance of definite argyria after the application of silver for relatively short periods^{1, 2} suggest that the patient has received some other silver medication during earlier periods of his life.

Only very few instances of argyria of the female genital tract have been described.^{3, 6, 13} In some cases of general argyria the ovaries and the uterus were found to be affected. Local application of silver solutions to the cervix or cervical polyps⁴ resulted in local discoloration, which was shown to be due to argyria. A study of available literature failed to disclose a report of argyria due to metallic silver slowly dissolving in the uterine cavity. No record was found of argyria of the Fallopian tube. Therefore the following observation seems worthy of being put on record.

P. S., a 58-year-old white female, entered the hospital on March 5, 1941, because of something protruding from the vagina and right lower quadrant discomfort. These symptoms were present for three months. Her menses had been regular every twenty-nine days, of four to five days' duration, moderate flow, no dysmenorrhea, and had ceased in 1933. There had been no bleeding up to one week before admission, when it appeared and continued until entrance into the hospital. It was this symptom that alarmed her and caused her to come for treatment. There was nothing of significance in her past history, except that twenty-seven years ago a cervical silver pessary had been inserted. She was a para iv, gravida iv, with no pathology during her pregnancies or deliveries.

*Aided by a grant of the Dazian Foundation for Medical Research.

Her temperature and pulse were normal; blood pressure was 160/100. Vaginal examination showed a large, edematous, pedunculated, mucous polyp protruding from the vaginal introitus; a relaxed pelvic floor; no palpable uterine or adnexal pathology. Rectal examination found no palpable or visible pathology. Speculum showed the atrophic cervix with the polyp protruding from it.

Physical examination revealed no other abnormalities. The skin showed no evidence of pigmentation.

Laboratory Findings.—Blood count, urinalysis, and blood chemistry determinations were normal. The complement fixation and flocculation tests for syphilis were negative. X-ray examination of the pelvis reported the presence of a metallic foreign body (pessary) within the lesser pelvic cavity, most likely within the uterus.



Fig. 1.

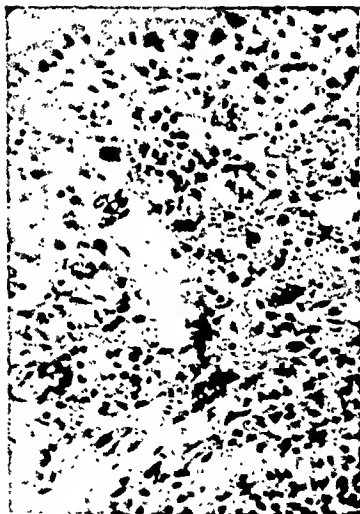


Fig. 2.

Fig. 1.—Uterus with pessary and cervical polyp.

Fig. 2.—Uterine endometrium showing the surface epithelium and the silver deposits in the stroma. $\times 150$.

On March 8, 1941, a vaginal hysterectomy and perineorrhaphy were performed. The operative findings were several small intramural fibroids, a pedunculated cervical polyp, relaxed pelvic floor. When the uterus was opened, a Y-shaped pessary was found imbedded in the endometrium, and about 3 or 4 mm. above it a streak of dark material was seen in the cut myometrium.

Patient had an uneventful postoperative course and was discharged on March 20, 1941.

Examination of Specimen.—The specimen (Fig. 1) consisted of a uterus with cervix measuring 85 by 40 by 30 mm. The serosa showed no essential abnormalities. The myometrium was light brown in color; it measured up to 15 mm. in thickness. An intramural fibromyoma

measuring 15 mm. in diameter was present. The endometrial cavity measured about 40 by 20 mm. It contained a Y-shaped dark metallic foreign body (intrauterine pessary); the stem measured 18 mm., each of the two arms 19 mm. in length. One arm was deeply embedded in the left uterine horn. The endometrium measured up to 2 mm. in thickness; it showed a diffuse black discoloration. In the lower segment there was an ulcer measuring 18 by 4 mm. which was apparently produced by the stem of the pessary. The cervix showed a pedunculated polyp, measuring 11 by 7 by 4 mm. with many cysts filled with mucoid material on the section surface.

Microscopic Findings.—The surface of the endometrium was lined in some places by columnar epithelium, but in most places it was bare. In the stroma and in the superficial layers of the myometrium, there were present deposits of a brown and black granular material (Fig. 2). The granules were very fine and widely scattered. The surface and glandular epithelium was completely free of the deposits. Most of it

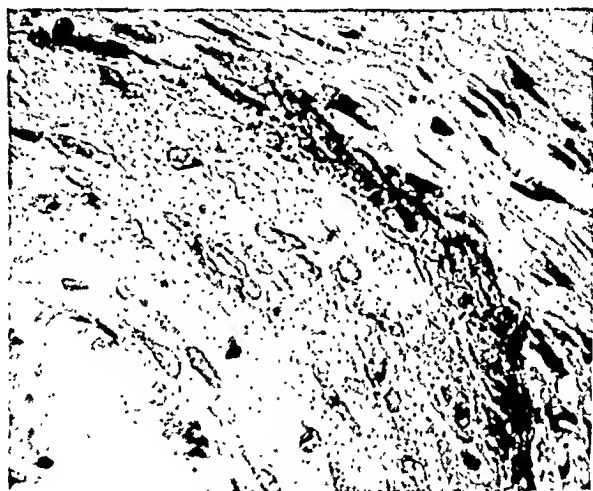


Fig. 3.—Wall of a blood vessel in the myometrium with massive deposits of silver granules in the adventitia. $\times 375$.

was present in the connective tissue of the areas laid bare by the absence of the endometrial epithelium. It was found in the cytoplasm of the fibrocytes and in the intercellular fibers and spaces. Small amounts were seen in the endothelial cells lining lymph spaces. Some tissue spaces were dilated and filled out by cloudy light brown masses. High power magnification revealed them to be composed of very fine pigment granules. The coarser granules were brown or black in color. In some areas the material was seen in the connective tissue not in a granular form but forming fine threads resembling microscopic sections in which fibrils were stained with a silver stain. Smooth muscle cells in the myometrium were by far less intensely affected than the connective tissue cells. The pigment seen in the endothelial cells of small blood vessels was situated almost exclusively on the outer side of the nucleus away from the lumen. In the adventitial layer of the blood vessels the deposits were very dense, forming dark rings (Fig. 3). The epithelium and the connective tissue of the cervix were free from the granules.

In the intramural portion of the Fallopian tube the epithelium was free from deposits. The borderline between epithelium and connective

tissue was marked by an accumulation of granular pigment in the connective tissue cells (Fig. 4). The infiltration was less intense in the outer parts of the submucosa and still more dilute in the surrounding muscular tissue.

The appearance of this material, its localization, the lack of inflammatory reaction around the deposits suggested that it consisted of silver or a silver compound.

A portion of the pessary was examined chemically and found to give the characteristic reactions of silver.

Histologic sections of the uterus and tubes were stained with polychrome methylene blue and studied in the dark field.^{8, 9} With this method a very much larger number of granules was visualized. The granules had a bright shine of yellow tinge which was described to be typical for silver particles.

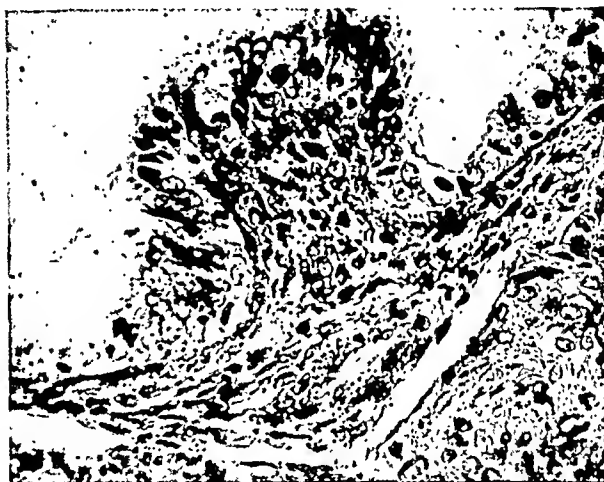


Fig. 4.—Section of Fallopian tube with deposits of silver granules in the subepithelial layers. $\times 265$.

Seven per cent nitric acid did not dissolve the deposits, but application of 30 per cent nitric acid (for twenty minutes) dissolved some of the granules. When, after washing out the acid, ammonium sulfide was applied, some of the remaining granules turned dark olive brown in color (silver sulfide). Five per cent solution of sodium cyanide dissolved the granules in ten to thirty minutes. When the specimen was treated first with Lugol's solution of iodine and then with 2 per cent sodium cyanide, the partly dissolved granules reacted with the iodine turning yellow (silver iodide). Staining for iron pigment (potassium ferrieyanide method) yielded a completely negative result.

These tests established the diagnosis of argyria of the uterus and the tubes. It has to be assumed that either the normal secretion of the uterine glands or the tissue-fluid oozing from the surface bare of its epithelium or both are capable of corroding silver if sufficient time elapses. The dark surface of the pessary proves that it was covered by an oxide. The material has been absorbed into the wall of the uterine cavity and into the wall of the tubes. In both it has been deposited mainly in the connective tissue, a characteristic finding of all forms of argyria.

Argyria of the uterus and tube is of relatively little clinical importance in itself. However, in the connective tissue of the cutis only a definite amount of silver can be stored, otherwise general argyria may appear. By any former application of silver the deposits may be close to this threshold. Then the additional absorption of a relatively small amount of silver may lead to discoloration of the skin. In cases of otherwise unaccountable argyria in women, the possibility of absorption from a silver pessary should be kept in mind.

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MALIGNANT MESONEPHROMA OF THE OVARY

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THE term mesonephroma defines a group of ovarian tumors classified by Schiller¹ as having characteristic histologic features and said to arise from heterotopic rests of mesonephric tissue. In Schiller's original series of 10 cases, the age of the patients varied from 8 months to 69 years. Because of the findings and course in 7 of the 10 cases described, he believed that, clinically, the mesonephromas should be considered malignant tumors. Schiller also noted that only one of his cases appeared solely in the left ovary. This is in keeping with Popoff's² observation that embryologic defects in animals and man are more often found on the right side than on the left. Jones and Seegar³ consider this evidence of the possible embryonic if not mesonephric origin of the tumor.

In the 6 cases reported by Jones and Seegar, the age of the patients varied from 41 to 72 years. Two of these tumors were malignant and 4 benign. In only one of these cases was the tumor solely in the left ovary. Jones and Seegar also pointed out that there were no symptoms by which these tumors could be clinically distinguished from other ovarian neoplasms.

Tuta and Siebel⁴ recently added a case arising from the left ovary of a 49-year-old woman. In this instance the tumor was malignant.

REPORT OF A CASE

A 62-year-old white, married woman (S.B., Path. S.P. 41-1356) was admitted to the Jewish Hospital of Brooklyn on April 17, 1941, complaining of backache and constipation of many years' duration, loss of 10 pounds in weight within the past three months, and a bloody stool two weeks prior to hospitalization. Her last menstrual period occurred six years ago. Examination revealed a tense, movable, nontender cystic mass occupying the hypogastric region.

At operation a large cyst of the left ovary was found. The tumor was adherent to the sigmoid, rectum, uterus, and broad ligament. The contents of the cyst were aspirated before removal and thin, grayish fluid was obtained. Inside the cyst wall was a cauliflower-like growth



Fig. 1.—Tumor showing solid and cystic structure.

about 5 cm. in its greatest diameter. The right tube and ovary presented normal senile changes. The abdominal viscera were explored and no metastatic foci were found. A supracervical hysterectomy and bilateral salpingo-oophorectomy was performed after freeing the wall of the cyst from adhesions.

PATHOLOGIC REPORT

A. Gross Description.—The specimen was a pear-shaped uterus, amputated above the cervix, with attached Fallopian tubes and ovaries. The anterior surface of the uterus was smooth and glistening; the posterior surface was roughened. There was a soft endometrial polyp projecting into the uterine cavity. The myometrium contained several small leiomyomas. The Fallopian tubes and right ovary presented nothing of note. The left ovary was intimately adherent to the Fallopian tube. The ovary was represented by a cystic mass measuring 10 by 8 by 2.8 cm. The external surface was pink gray, smooth, and

glistening in some areas and roughened by fibrous tags in others. Projecting into the lumen and firmly adherent to the wall were several large, soft, polypoid and cauliflower-like gray, red and yellow nodules which measured up to 7 by 5 by 2 cm. The cut surfaces of these masses were

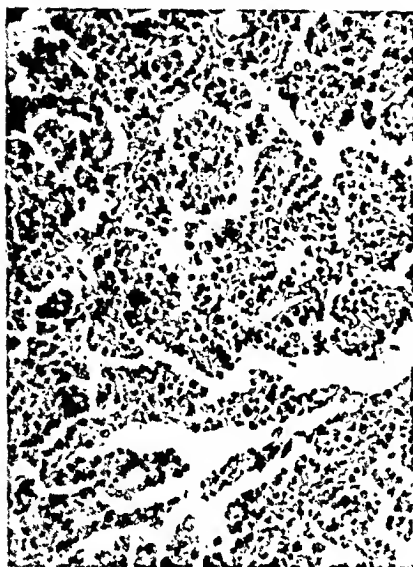


Fig. 2.

Fig. 2.—Section showing glomerularlike formations. (H. & E., $\times 250$.)

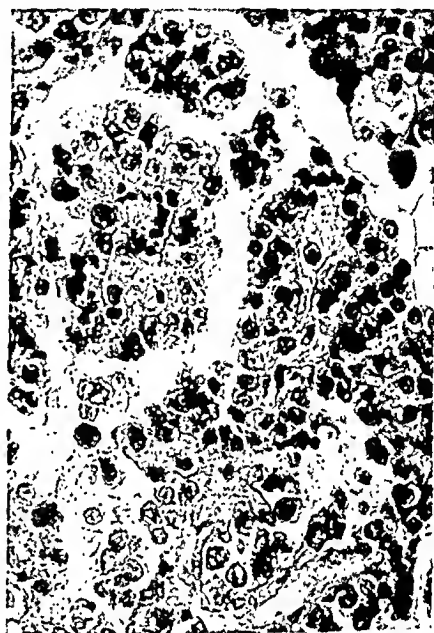


Fig. 3.

Fig. 3.—Same as Fig. 2, $\times 525$. Note capillary in glomerularlike tuft.



Fig. 4.—Section showing irregular lumina lined by cells with projecting nuclei. (H. & E., $\times 185$.)

composed of opaque stalks of gray yellow translucent tissue. The remainder of the inner lining of the cyst was gray, smooth, and glistening and occasionally showed small papillary projections of yellow tissue similar to the large mass described above.

B. Microscopic Description.—Preparations from the uterus, right ovary, and Fallopian tubes were not remarkable. Preparations from the cystic and papillary portions of the tumor showed numerous papillary intracystic formations composed of irregular projections covered by low cuboidal cells or endothelial-like cells having sparse cytoplasm and projecting nuclei. In places small capillary loops were present within such papillary projections. Some of these structures closely resembled rudimentary glomeruli. There were also many scattered small and large irregular spaces lined by markedly flattened cells or by the endothelial-like cells with projecting nuclei and scanty cytoplasm. Some of these tubules contained homogeneous pink- and lavender-staining material. In the solid portions of the tumor many more irregular various-sized tubules were present, some of which were almost completely filled with

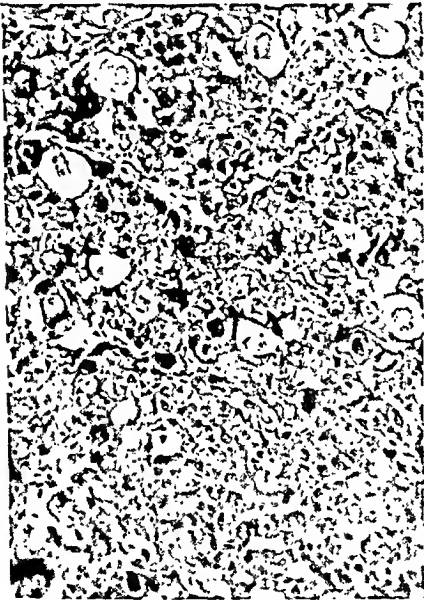


Fig. 5.



Fig. 6.

Fig. 5.—Section showing lack of differentiation, hyperchromatism, and giant cells. (H. & E., $\times 250$.)

Fig. 6.—Same as Fig. 5, $\times 525$.

pink- and lavender-staining material. In other areas, however, the cells appeared in small nests separated by broad bands of dense collagen. The cells showed marked variations in size and shape and contained deeply staining nuclei. Some were giant cells and contained more than one nucleus. Nucleoli were likewise prominent in some of these cells. There were also groups of large polygonal cells having foamy cytoplasm and relatively small vesicular nuclei. The cyst wall consisted of dense hyalinized fibrous connective tissue and was lined by low cuboidal cells.

COMMENT

This cystic neoplasm fulfills the criteria of mesonephroma ovarii as defined by Schiller and others. The tumor contains structural units resembling mesonephric glomeruli, and in some, well-defined capillary

loops were seen. In places, cells lining the cystic spaces contain sparse cytoplasm and buttonlike projecting nuclei common to the flat cells of the visceral layer of Bowman's capsule. Well-defined tubular structures are also seen. In addition, the histologic picture shows definite evidence of malignancy, which also is in keeping with most of the tumors of this type previously described in the literature.

While previous observation suggests that mesonephroma ovarii arises usually on the right side, it is well to note that in this instance, the tumor appeared solely in the left ovary. However, definite conclusions as to the side of predilection, if any, should not be drawn until many more cases have been reported.

With this case included, 12 of 18 patients were women aged 40 or over. This would seem to indicate that mesonephroma ovarii is a tumor usually occurring in the later years of life, but again too hasty conclusions should not be drawn until the series is larger.

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BILATERAL TUBAL PREGNANCY

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IT IS our purpose to add another instance of bilateral tubal pregnancy to the growing list of accepted cases in the literature.

Fishback¹ emphasized the importance of the correlation of the clinical data with the description of the fetuses, or parts thereof found, as well as the placental elements. He further gave a review of the literature, listing 75 acceptable cases to which he added one, bringing the total to 76 cases. Torpin² quoting Fishback's series added another case bringing the total to 77 cases. He emphasized the necessity of considering bilateral simultaneous tubal pregnancy as a form of double ovum twin pregnancy, similar to the so-called heterotopic pregnancy of which there are some 300 cases in the literature. Behney and Hanes³ reported a case of bilateral tubal gestation in which they felt that the two pregnancies must have occurred within a comparatively short interval of time, though they might not have been viable simultaneously. The point of inspecting both adnexa at the time of operation for tubal pregnancy is brought out. Lee and Stone⁴ reported a subsequent case, bringing the total number of cases in the readily available literature to 80. McIlrath⁵ reported a case of bilateral tubal pregnancy which was not proved by microscopic examination.

CASE REPORT

A negro woman, 26 years of age, married, was admitted to the Roper Hospital on Feb. 25, 1941, at 12:04 A.M. with the complaint of "pain

in stomach." She had been well until about four hours prior to admission, at which time there was sudden onset of cramplike pain in the right lower abdominal quadrant just above the inguinal ligament. The patient vomited once. She did not faint but suddenly felt very weak. The pain remained cramplike and intermittent in quality but had subsided considerably in intensity by the time the patient was first seen by the house staff.

Review of the menstrual history revealed that the menses had begun at the age of 13 years, had been fairly regular at twenty-eight to thirty-day intervals, and with an average duration of four days. The patient had had two labors at term; both children were living and well, the youngest was two years of age. The last menstrual period had begun Feb. 5, 1941, lasting eight days. The preceding periods in January and December had been uneventful and had lasted four to five days each. On the day before admission she suddenly began to flow quite profusely; this had slackened by the time the patient was first seen. No history of dysuria or other symptoms referable to the genitourinary tract.

Physical examination revealed a drowsy young negro woman lying quietly in bed complaining of air hunger. The respirations were of sighing quality at times. The pulse was 120, rapid and thready. Respirations were 40 per minute. Blood pressure was 56/36. The skin was dry and cool to the touch, and there was slight rigidity of the abdomen, particularly over the right lower quadrant. Pelvic examination revealed a moderately relaxed perineum. Bartholin's and Skene's glands were not remarkable. The cervix was parous in type, softened in consistency and dark red in color. There was some bloody discharge from the external os. The uterus was in second degree retroversion and slightly enlarged. There was a questionable mass in the right fornix. Hemoglobin was 6 Gm.; white blood count, 18,000, with 83 per cent polymorphonuclear leucocytes.

The diagnosis of ruptured ectopic pregnancy was made, notwithstanding the lack of history of a missed period. The patient was given 500 c.c. of a 10 per cent glucose solution, followed by 500 c.c. of citrated blood during the course of the operation. Under ether anesthesia, the abdomen was opened through a lower midline incision. The peritoneal cavity was found to contain an estimated 2,000 c.c. of fluid and clotted blood. The right Fallopian tube was distended in its distal half to a diameter of about 4 cm. and blood was dripping from a small rent on the posterior aspect of the swollen portion. The left tube presented a nodular swelling in its midportion, about 2 cm. in diameter, and was of a dusky red color as seen through the serosa. The serosal surface of the right tube and cortical surface of the right ovary appeared smooth and regular; the corresponding surfaces of the left side showed a few old fibrous adhesions of delicate character. Both ovaries were of average size, as was also the body of the uterus. Both Fallopian tubes were removed and the abdomen closed without drainage. No corpus luteum was identified in either ovary at the time of operation.

The right Fallopian tube showed a prominent dilatation of the distal half, and measured 3.0 cm. in diameter. There was a blood clot on the serosal surface and a perforation on the posterior aspect of the tumefaction from which blood was oozing. Transverse section through the middle third revealed a centrally situated amniotic sac, measuring 1.5 cm. in diameter, containing a small embryo. This was surrounded

by a zone of hemorrhagic and gray tissue which appeared to have eroded the tubal wall posteriorly at the point of perforation.

The left Fallopian tube showed a nodular dilatation of its middle third, measuring 2.2 cm. in diameter. The fimbriated extremity was contracted and distorted by well-formed fibrous adhesions. Transverse section through the nodular swelling showed the lumen to be distended by a blood clot of lighter brown color than that seen in the case of the right tube. One segment of the circumference of the wall appeared eroded and paper thin.

Microscopic section of the dilated right Fallopian tube, which was seen grossly to be ruptured, showed the lumen to be occupied by fresh blood clot and a scattering of polymorphonuclear leucocytes, enmeshed in which were fairly numerous chorionic villi with two layered trophoblastic covering. Some few villi were necrotic. There was destructive infiltration of the musculature of the wall by chorionic villi and trophoblasts. Necrosis with loss of continuity of the muscle elements and

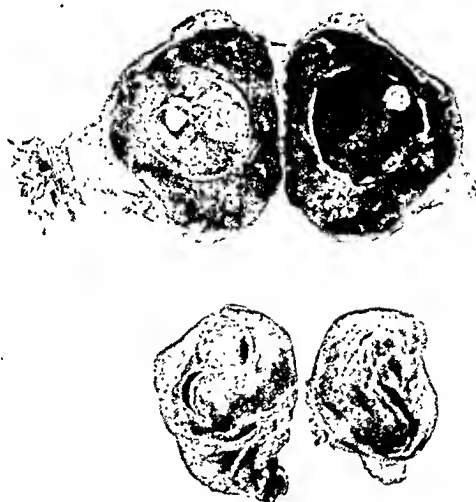


Fig. 1.—Above: Right tubal gestation, ruptured. Below: Left tubal gestation, regressing.

fibrous stroma and fresh hemorrhage on the serosa attested to complete perforation of the tubal wall. Adjacent to this rent, replacing necrotic musculature, was a fibrinoid zone. The muscle fibers of the wall showed hypertrophy and the intervening supportive stroma was edematous and infiltrated by round cells; there was early purulent exudation present about vessels. On the serosal surface an occasional disrupted fairly well-vascularized fibrous adhesion, partially covered by hyperplastic mesothelium, was noted.

Microscopic section of the left Fallopian tube showed the dilated lumen to be occupied by clot in which the silhouette forms of necrotic chorionic villi and some cell forms, judged to be trophoblasts, were discernible. The latter showed deep infiltration into the wall. Around the periphery was a fibrinoid layer and focal aggregates of xanthic macrophages containing blood pigment. In association with the latter were proliferating fibroblasts, evidence of early organization. In one zone the tubal wall was eroded and reduced to a very narrow confining zone

of muscle and fibrous tissue. Inflammatory round cells were scattered in foci throughout the wall and serosal adhesions were more pronounced than in the case of the foregoing tube. Incorporated in one section was the fimbriated extremity of the tube showing elubbing of the mucosal villi, fibrous tissue increase and inflammatory round cells in the stroma of the mucosa.

DISCUSSION

As seems to be the general rule in cases of bilateral tubal pregnancy, there was no indication from the history or physical findings in this case that such a condition existed, though the patient was evaluated as a relatively intelligent woman.

The question arises as to whether or not these two tubal pregnancies were viable simultaneously. The fact that the left tube was filled with older blood clot, contained necrotic chorionic villi, and showed blood pigment phagocytosis in its wall along with evidence of early organization of the clot would indicate regression, the age and duration of which are controversial. It is notable, however, that organization, as evidenced by fibroblastic activity, was very early, certainly not advanced. Such fibrous tissue increase in the tubal wall that existed appeared to be a part of the same inflammatory scarring reflected in the serosal adhesions found in the case of both tubes and mucosal stroma of the left. It further seems that with the marked degree of destruction and thinning out of the wall of the left tube that was present in association with trophoblastic penetration, reparative organization would certainly have been more conspicuous if sufficient time had elapsed. All factors considered, the evidence for simultaneous viability of these tubal pregnancies at one time appears presumptively strong. It is unfortunate that conditions at the time of operation did not allow for closer scrutiny of the ovaries for corpora lutea. It is considered significant that both tubes in this case showed old fibrous adhesions and the left showed the fibrous relic of endosalpingitis as well. This recalls the part played by inflammatory scarring, acting as a mechanical hindrance to the passage of the fertilized ovum, in the causation of tubal pregnancy.

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DESMOID TUMOR OF THE BACK

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SINCE desmoid tumors in some instances may resemble sarcomas, a desmoid fibroma of the back clinically suspected of being a metastasis from an anaplastic uterine sarcoma removed eleven and one-half years before, presents an interesting case for clinical and pathologic correlation.

The term "desmoid" was first applied by Johannes Müller in 1838 to designate a peculiar hard tendonlike tumor. The nature of a desmoid tumor is that of a benign fibroma arising from musculoaponeurotic structures, or the endomysium according to Ewing.³ Some of the tumors classified as desmoids may be neurofibromas, according to Ewing³ and Penick.⁹ Desmoid tumors are most commonly found in the abdominal wall of women who have borne children, although they have been observed in nulliparous women, and rarely in the abdominal wall of men. Penick,⁹ from an analysis of reviews covering over 500 desmoids, found 17 which occurred in postoperative scars. The postoperative cases predominated in females and usually occurred about one year after operation.

Desmoids are found much less frequently in locations other than the abdominal wall. Nichols,⁷ in a series of 31 desmoid tumors at the Mayo Clinic from 1910 to 1922 inclusive, found 6 instances in muscles outside of the abdominal wall. Five cases were suspected of being sarcomas, the other was in a woman, 36 years of age, in whom a radical mastectomy had been performed for the removal of a tumor in the left lower inner quadrant of the breast. Mason⁵ reported a series of 27 desmoid tumors at the Mayo Clinic during the years 1923 to 1929, inclusive. Nine of these tumors were located in relation to various muscles other than the abdominal group. Bellanger¹ reported a muscular fibroma, developing at the level of the scapular insertion of the serratus magnus muscle, and briefly reviewed several cases in the literature involving muscles other than abdominal.

CASE HISTORY

A widow, 51 years of age, entered the Grant Hospital on Jan. 11, 1928, complaining of lumbar pain of several years' duration. A diagnosis of a uterine fibromyoma had been made several months before. She had had 3 pregnancies and one miscarriage. The red cell count was 3,550,000. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed by Dr. E. W. Fischmann. A gross diagnosis of a soft degenerated uterine fibromyoma was made. There were polypoid masses which filled the uterine cavity.

Microscopic examination showed anaplastic sarcomatous areas in a fibromyoma with numerous large hyperchromatic tumor giant cells with multiple prominent nucleoli. There were areas resembling the ordinary

benign fibromyoma with cystic degeneration and hyalinization. There were also large hyperchromatic tumor cells embedded in dense connective tissue.

On Aug. 1, 1939, the patient entered the Grant Hospital for the removal of an egg-sized mass on the left side of her back. She first noticed the lump seven months before and at that time it was about the size of her thumb. She had occasional slight pain. The tumor mass was slightly movable and unattached to the skin. At operation it was found



Fig. 1.—Desmoid tumor showing interlacing bands of dense fibrous tissue and irregular softer areas containing muscle fibers.

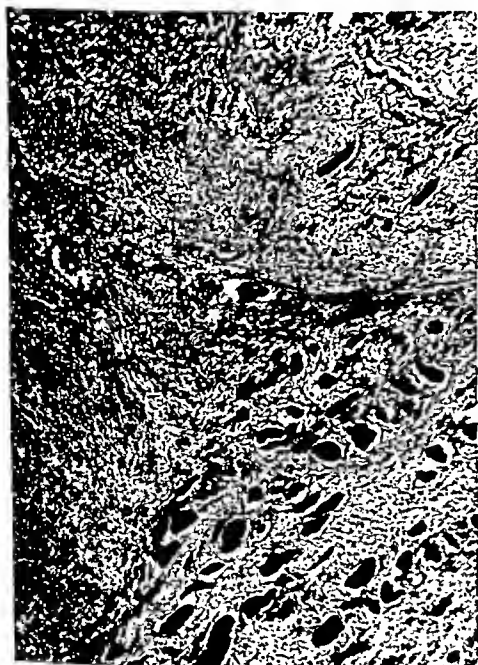


Fig. 2.



Fig. 3.

Fig. 2.—Showing moderately cellular connective tissue widely separating muscle fibers. Mallory's phosphotungstic acid hematoxylin stain. $\times 40$.

Fig. 3.—A higher magnification showing the muscle fibers separated by desmoid tissue. Mallory's phosphotungstic acid hematoxylin stain. $\times 112$.

to lie on the left side near the spinal column over the twelfth rib. A transverse incision was made through the superficial fascia and then through the aponeurosis of the latissimus dorsi muscle. The tumor mass was found to be intimately attached to the underlying sacrospinalis and posterior inferior serratus muscles. The surgical specimen was very hard and measured 6 by 5 by 4 cm. It was partially covered by muscle tissue. The surfaces made by sectioning showed interlacing bands of dense white tissue and irregular softer brown areas particularly at the periphery.

Microscopic examination showed a moderately cellular connective tissue through which were scattered isolated muscle fibers. With the Van Gieson, Masson trichrome and Perdrau silver stains, the arrangement of the connective tissue elements was clearly outlined. The connective tissue cells displayed no nuclear anaplasia. The Masson trichrome and Mallory's phosphotungstic acid hematoxylin stains showed the muscle fibers standing out in sharp contrast with the cross-striations of many of the muscle fibers showing distinctly. In some of the fibers there were degenerative changes and in others wide separation of the myofibrils.

DISCUSSION

The histologic examination of the tumor involving the back muscles revealed the structure to be a typical benign desmoid without relation to the uterine sarcoma removed previously. If the connective tissue had been very cellular in character, the question of a sarcoma might readily have arisen. Waugh¹¹ stated that recent unpublished studies by Pearman and Mayo indicated that the desmoid type of tumor is definitely benign. Recurrences are attributed to incomplete removal at operation. Marlow⁴ reported a tumor in the trapezius muscle of a woman 26 years of age which was clinically a desmoid, but the very cellular character of the connective tissue suggested a sarcoma. There was no recurrence after eight years. Roentgen ray therapy was given because of the suspicion of a fibrosarcoma. Donald and Caylor² reported a desmoid tumor having cellular areas considered sarcomatous. Warren and Sommer,¹⁰ in a study of fibrosarcomas of the soft parts, classified desmoid tumors as being histologically sarcomas. The peculiar localization of the majority of desmoid tumors in the musculoaponeurotic structures of the abdominal wall in women who have borne children suggests that trauma may be a predisposing factor and that a hematoma in the muscle may be the initiating factor.

The uterine sarcoma, in the case we are reporting, was thought to arise in a pre-existing fibromyoma and to be of myogenic origin. Ewing³ and Novak⁸ discussed the difficulties connected with determining whether a malignancy develops as a transformation of a pre-existing benign fibromyoma or whether it was malignant from the beginning. The large hyperchromatic tumor cells in the uterine sarcoma gave the impression of dealing with a very active malignant process, if we depend only on histologic structure as a criterion for malignancy. However, metastases are very rare in malignant uterine myomas, Ewing³ having encountered only 3 such cases with generalized spread. According to Novak,⁸ the type arising in uterine myomas is in general less malignant than from the endometrium or myometrium. McFarland⁶ concluded that with malignant myomas metastases constituted the only proof of malignancy.

He also cited a case, referred by Dr. Jonathan Wainwright, of a patient who had a "suspicious fibroid" removed and in whom there later occurred metastases in the neck, thigh, and abdominal wall. The metastases were removed surgically and the patient was alive twelve years following the hysterectomy.

SUMMARY

A desmoid fibroma involving the sacrospinalis and posterior inferior serratus muscles of the back is reported. A supraervical hysterectomy was performed eleven and one-half years before with removal of an anaplastic uterine sarcoma. The patient is alive and well thirteen and one-half years following the hysterectomy, and there is no recurrence from the uterine sarcoma or the desmoid tumor of the back. Clinically the desmoid was suspected of being a late metastasis from the uterine tumor.

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GANGLIONEUROMA COMPLICATING PREGNANCY

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GANGLIONEUROMAS have been located in all parts of the body, but they are most prominent in the retroperitoneal spaces of the thorax and abdomen. In this report we are chiefly concerned with those tumors found in the abdomen and pelvis.

Beneke reported the first case of pelvic retroperitoneal ganglioneuroma in 1898; only 13 have been reported up to 1940 according to Turunen. Pick and Bielschowsky in 1911 revealed the true relationship between ganglioneuromas and the sympathetic nerve elements, and classified true neuromas on an embryonic basis. They named them embryonic sympathetic gangliomas. These tumors are now considered to develop at the site of cell nests that have become displaced during embryonic life and therefore are congenital in origin. They are seldom diagnosed before operation, and at times after operation they are diagnosed as fibromas, liposarcomas, or fibrosarcomas.

According to Evans and Francona, the tumor is more frequent in women than in men and more in the left side of the body than the right side. It is more prominent in the first twenty years of life. The

majority of these tumors are benign and cause symptoms because of pressure on the surrounding vital structures. These tumors are very slow growing and have been known to have been present for years with no tendency to become malignant.

Technical difficulties are usually encountered in the delivery of the tumor, since it tends to be firmly adherent to the adjacent structures. Of the 13 cases reported (Turunen), 8 patients were operated upon and 5 tumors were discovered at post mortem.

CASE REPORT

M. B., aged 20 years, white, unmarried, was admitted to the Booth Memorial (Salvation Army) Hospital in June, 1940. Her past history showed that her health had generally been good. She was nervous and had had indigestion for the past four or five years. She had the usual childhood diseases and had had no operations. She was seen some time ago by a physician who told her that she had a tumor of the ovary, and he advised operation. Family history was essentially negative. Her menstrual periods, which began at 15 years of age, occurring every thirty days, were regular, of moderate flow, and there was no dysmenorrhea. The last menstrual period was Jan. 6, 1940.

Her general physical examination was essentially negative. Pelvic examination showed a nulliparous vagina, with no evidence of infection. The pelvis was filled with a hard lobular mass rather fixed to the sacrum, about the size of a large grapefruit, which did not seem to be connected to the uterus. The uterus was enlarged to about a five or six months' gestation. The cervix was pulled up under the symphysis. X-ray of the abdomen showed the fetus outlined rather high in the abdomen, but no definite outline of a tumor mass could be made out. Pelvic measurements were within normal limits. Laboratory findings showed a negative Kahn test. The red blood count was 4,100,000 and the white blood count was 7,900.

Preoperative diagnosis was: a pregnancy of twenty weeks' duration, and dermoid cyst filling the pelvis.

At operation a large retroperitoneal mass was found filling the pelvis. It was fixed to the sacrum and to the iliac vessels and nerves. It was impossible to ligate the entire wide pedicle in one piece, and since the tumor seemed to involve the iliac vessels, most of it was removed, leaving a thin shell of tumor attached to the sacrum.

The specimen was examined by Dr. Sam Katz of the Booth Memorial Hospital Pathological Department.

The specimen consisted of a lobulated tumor, pale yellow, firm, and cutting like gristle. The tumor resembled a lipoma except for the firmness. On microscopic section, the connective tissue of the tumor was interposed with numerous cellular structures. Under special stain the larger and smaller groups of large round ganglion cells were seen. In general the ganglion cells had only one nucleus. Occasionally one found a double nucleus. The ganglion cells were well developed, sympathetic ganglion cells.

Postoperative diagnosis was a twenty weeks' gestation, and presacral ganglioneuroma.

The postoperative course was smooth and the pregnancy continued uninterrupted. Rectal examination on Aug. 13, 1940, showed a right posterior pelvic mass somewhat irregular and fixed to the pelvic wall,

which seemed to obstruct the inlet. The patient was permitted to go to term at which time a cesarean section was considered.

The patient began having contractions on Sept. 17, 1940. On examination it was felt that the pelvic mass previously palpated would not cause enough dystocia to obstruct labor. Labor was permitted to progress and she was delivered of a 6 pound 9 ounce female infant by means of perineal forceps over a right mediolateral episiotomy. No unusual difficulty was encountered in the delivery.

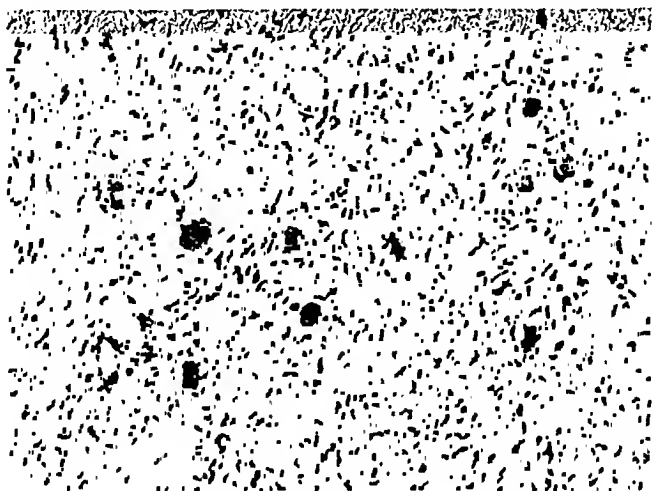


Fig. 1.—Section from tumor showing typical ganglion cells. Low power ($\times 145$).

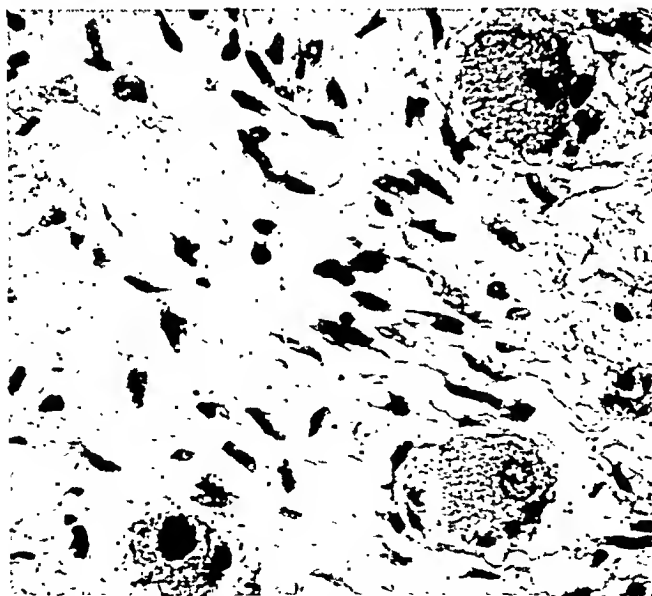


Fig. 2.—High power of section from tumor ($\times 630$).

The post-partum course was uneventful. On Sept. 22, 1940, a rectal examination revealed the mass to be smaller. Some induration could be felt on the right side. The patient was last seen Nov. 1, 1940, at which time the pelvis was normal and there was no evidence of any mass present. She had no symptoms referable to her pelvis.

COMMENT

This presents an unusual and interesting case. Very few cases of this tumor have been reported in the literature, but as mentioned before, it is probable that many have not been diagnosed and have found their way under the classification of other tumors such as fibromas, lipomas, liposarcomas, and fibrosarcomas. Because of the rarity of the condition a correct preoperative diagnosis is difficult, and the more common conditions are usually considered. The most interesting feature of the case was the complete disappearance of the remnants of the tumor after the patient had delivered. When the patient was last examined, she presented a normal pelvis.

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MONOAMNIOTIC TWIN PREGNANCY

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THE following case seems of interest because twins so rarely develop in one amniotic sac.

A white primipara, aged 27 years, entered the private service of Dr. Frank W. Lynch in the University of California Hospital on Dec. 1, 1940, in premature labor. Her expected date of confinement was Feb. 15, 1941; her last menstrual period May 8, 1940. The prenatal course had been uneventful. The Wassermann test was negative and the pelvis was normal. Twins had been suspected in the early months of pregnancy because of the relatively large size of the uterus, but the rate of growth then slowed down and the possibility was discarded. The family history revealed that the patient's maternal great aunt had twins but no other twins occurred in either the patient's or her husband's family.

On entering the Hospital, the patient stated that she had not felt any fetal movements for several days and that, four hours prior to entry, fleeting uterine contractions had begun, associated with suprapubic pain. These contractions had increased steadily in severity and at the time of examination were severe and occurred every one and one-half to two minutes. An excessive bloody show occurred as the patient entered the Hospital.

Physical examination disclosed: a uterus two fingerbreadths above the umbilicus; no fetal heart could be heard. The uterus was not unusually hard or tender between contractions. On rectal examination, the cervix was dilated 4 cm. with the membranes intact and a footling presentation.

Temperature, blood pressure, pulse, and respiration were normal. The hemoglobin was 83 per cent (12 Gm.). The blood type was IV (Moss).

The patient was given nitrous oxide and oxygen with her pains, and because vaginal bleeding persisted, a vaginal examination was made which showed a cervix completely dilated with membranes bulging through the os. These were ruptured artificially, when the lower edge of the placenta could be felt at the left posterior margin of the dilated cervix. Because vaginal bleeding still persisted, the feet were brought down rapidly and the fetus readily delivered as a breech presentation; the second, and much smaller, fetus, was expressed by pressure on the fundus. The first infant was a macerated premature fetus and weighed 1,300 Gm. The second infant was flat, almost papyræus. It weighed



Fig. 1.

but 185 Gm. and measured $16\frac{1}{2}$ em. from crown to rump. Considerable bleeding occurred, both immediately after the delivery of the infants and of the placenta, the total blood loss being estimated at 1,200 e.e. Consequently, intravenous (10 per cent) glucose was administered to the patient immediately after the second stage, 1,000 e.e. in each antecubital vein followed shortly by a transfusion of 750 e.e. of citrated blood. The patient's condition was good throughout with no evidence of shock.

The placenta measured 22 by 16 by 2 em. in size and weighed 720 Gm. The membranes were intact, but there was only one amnion and one chorion. No evidence of a partition between the two cords could be found, and, in addition, blood vessels from the larger of the two cords passed over the insertion of the smaller cord, entering the placenta in this area. The cords were inserted marginally, the one to the fetus papyræus being 55 cm. long and but 0.5 em. in diameter. The cord

to the larger fetus was 48 cm. in length and 1.5 cm. in diameter. At a distance of 30 cm. from the placenta, the two cords formed a complex true knot, while a separate true knot was present in the narrow cord in the same area. It seemed probable that the smaller fetus had died early in the pregnancy, possibly from a knot in its cord; and later had become entangled in the cord of the larger fetus, causing its death a day or two before the onset of the premature labor. The heart of the small fetus was grossly normal.

The patient's post-partum course was uneventful except for a rise in temperature to 38° C. on the third to sixth post-partum days, inclusive. Sulfanilamide was started on the fourth post-partum day, and coincided with a fall in temperature to normal within the next thirty-six hours. Blood counts on the first, fifth, and eighth post-partum days revealed the hemoglobin always above 80 per cent, and a maximum white blood count of 15,000. Urinalyses on the same days were within normal limits. The patient was up and in good condition on her tenth post-partum day.

DISCUSSION

A comprehensive review of the cases on monoamniotic twins was made by Quigley¹ in 1935. He stressed the rarity of the condition and states that from the time of the first case reports in the seventeenth century to 1935 he was able to find but 108 authentic cases to which he added one of his own. From the practical standpoint, the chief clinical interest is the danger of death of one or both fetuses from twisting or knotting the cords. This results in a high fetal mortality rate, but there is no more risk to the mother than in any other case of twin delivery. Quigley states that in 94 cases where it was possible to estimate mortality, the fetal death rate was 68 per cent. True knot formation was reported 58 times in the 109 cases, an incidence of 53 per cent. Eight monsters occurred in the series. Both twins survived in only 17 of the cases, a 15 per cent chance. (Since 1935, an additional case of survival of both infants has been reported by Parks.²)

Quigley, in stressing the rarity of this type of twins, states that he was able to find only eight cases reported in the American literature from 1835 to 1935. In reviewing the case reports in the American literature, we find this group is even smaller, since one of the cases included in Quigley's study (Boyd,³ 1883) is, in reality, a fetus papyraceus in a separate amnion. In fact, in describing the placenta of his specimen, Boyd states that "the fetal side shows the division in the amniotic sacs." In the six years since Quigley's study, we have found reports on three additional cases in the American and one in the British literature.^{2, 4-6}

Taken with the case report above, five cases in the past six years would indicate that the extreme rarity of monoamniotic twins is due, in part, to a failure in reporting or recognizing the condition after the delivery.

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PENETRATING CHORIONEPITHELIOMA WITH RUPTURE OF UTERUS AND FATAL INTRA-ABDOMINAL HEMORRHAGE

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THE literature on chorionepithelioma includes numerous examples of the bizarre course this interesting tumor may take. Devastating growth rapidity may be contrasted with instances of spontaneous disappearance of a tumor which is, microscopically, highly anaplastic. This is a report of a classic hydatid-mole-chorionepithelioma sequence with extensive penetration of the uterine wall, spontaneous rupture into the peritoneal cavity, and fatal hemorrhage.

The *Quarterly Cumulative Medical Index* for the preceding twenty years reveals several titles of questionably similar cases, but in each instance the report appeared in an obscure and inaccessible foreign publication. More instances of this sort have undoubtedly been observed but not reported.

CASE REPORT

Y. O., a 24-year-old Japanese female (Hospital No. 754817), entered the Los Angeles County General Hospital on March 9, 1941. With the aid of an interpreter, the following history was elicited:

The patient asserted that she had never been pregnant, but she passed a hydatid mole eight months before, in July, 1940. Subsequently, frequent irregular spotting and passage of clots occurred. On March 3, 1941, a week before entry, she was studied in another Los Angeles hospital because of an increase in the amount of spotting and frequent lower abdominal cramps; a positive urine Friedman test, radiologically negative lungs, moderately enlarged heart, and normal blood and urine were reported from this other hospital.

The patient was not acutely ill, and in good general physical condition. Blood pressure was 112/68. Bimanual pelvic examination showed the corpus uteri symmetrically enlarged to the size of a three to four months' pregnancy with a soft closed cervix and normal adnexal zones, with no masses. The red cell count was 3.8 million, hemoglobin 72 per cent, and leucocyte count 8,200, with a normal differential smear and a sedimentation rate of 26 mm. per hour. Urine examination was negative. A tentative diagnosis of threatened abortion was made, and she was placed on routine conservative therapy.

On March 12, 1941, at 12:40 P.M., three days after admission, the patient suddenly went into shock, the pulse became weak and flickering, and the blood pressure dropped to 60/0. The resident and I had made hospital rounds an hour before, and the patient seemed quite well at the time. The red cell count was 2.4 million, hemoglobin 32 per cent, and leucocyte count 6,400. Careful bimanual pelvic examination showed generalized abdominal tenderness; the uterus was only indefinitely palpable, the posterior vaginal fornix was soft, doughy, and seemed to bulge slightly. Shock therapy was administered immediately, including warm blankets, deep Trendelenburg position, and intravenous fluids.

The staff members concurred in a diagnosis of massive intra-abdominal hemorrhage, possibly due to rupture of the uterus.

Laparotomy was immediately performed, using field block procaine anesthesia with continuous oxygen inhalation. After incising the peritoneum, the abdominal cavity was found to be full of blood clots and liquid blood. A large mass of friable tumor tissue lay free in the cul-de-sac. There was a 4 by 2 cm. rent in the right superior aspect of the anterior wall of the uterus, with moderate bleeding issuing from the uterine cavity. A bluish nodule, 3 by 5 cm., occupied the anterior uterine wall near the cervix. On palpation, the entire uterus seemed very friable, the anterior wall and fundus were paper thin and mushy, and it was evident that hemorrhage could be controlled only by hysterectomy. The broad ligaments and adnexal attachments were rapidly

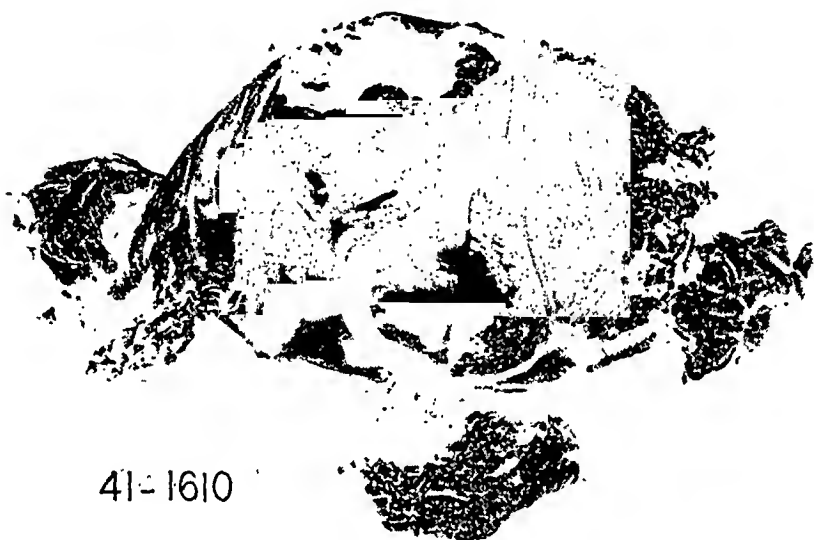


Fig. 1.—Specimen showing rupture of uterus due to penetrating chorionepithelioma.

clamped and divided, and because the cervix could be readily retracted upward, a cuff of vagina was incised around it and a rather easy total hysterectomy was performed. The vaginal opening was rapidly sutured, the adnexal stumps were joined and attached, and the abdomen was speedily closed. The patient was almost moribund upon arrival in the operating room, and despite a midoperative 500 c.c. citrated blood transfusion, continuous oxygen inhalation, and stimulants, she died during the course of the operation.

The pathologist reported: (1) Choriocarcinoma with perforation of the uterus; (2) decidual reaction in the endometrium; (3) hyperplasia of the myometrium typical of pregnancy; (4) theca lutein cysts.

Inability to communicate with the patient's family precluded permission for autopsy.

SUMMARY

A chorionepithelioma penetrated the uterine wall and resulted in spontaneous uterine rupture, extrusion of a free mass of tumor tissue into the peritoneal cavity, and fatal intra-abdominal hemorrhage.

THE "FROG" TEST (*XENOPUS LAEVIS*) AS A RAPID DIAGNOSTIC TEST FOR PREGNANCY*

PRELIMINARY REPORT

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DURING the past decade, two biologic tests for the determination of early pregnancy have come into general use, the Asehheim-Zondek (mouse) test and its Friedman modification (rabbit). The degree of accuracy of both of these tests is excellent, approximately 98 to 99 per cent, but the time element of ninety-six and thirty-six hours, respectively, is a drawback when speed is required in an emergency diagnosis of pregnancy.

In 1934 another biologic test, using the South African clawed frog, *Xenopus laevis*, was suggested.¹ Many different groups of investigators abroad have reported over 3,000 tests with 98 to 100 per cent accuracy in the use of this frog.² With this test for pregnancy, the time factor is greatly lessened (i.e., four to eighteen hours). The advantages of the frog test are obvious if the same accuracy and speed could be attained in America under different environmental conditions. We herewith report, for the first time in American literature, our findings with the frog test in 53 clinical cases of suspected pregnancy.

The "frog" test is based on the peculiar biologic function of the mature female *Xenopus* in that she carries eggs throughout the year, only extruding them with mating or after the injection of hormones peculiar to pregnancy. Since the test animals are kept isolated from the males, the extrusion of any ova following the injection of suspected urine becomes definitive for pregnancy (excessive gonadotropic hormone).

Apart from numerous experimental tests on known urines and various hormonal extracts³ 53 separate unknown urines were tested on the frogs. Parallel tests were performed on segregated rabbits using the same specimens of urine. The urines were from women who had either missed one menstrual period or had not missed any menses but suspected the possibility of conception. None of the patients could be clinically diagnosed as either pregnant or nonpregnant by physical examination.

The results of the tests are shown in Table I. It will be noted that out of 53 cases, 51 showed rabbit and frog in agreement, and two showed

*Supplies of frogs at present are limited considerably by present war conditions.
A detailed review of all the work on *Xenopus laevis* is in course of preparation.

TABLE I. COMPARISON OF FROG AND RABBIT TESTS

NO. OF TESTS*	XENOPUS (FROG) TEST	FRIEDMAN TEST (RABBIT)
18	18 negative	18 negative
33	33 positive	33 positive
1	+	-
1	+	-

*An additional case showed a discrepancy (i.e., frog negative and rabbit positive). However, since further specimens of this patient's urine were unobtainable, the disparity could not be checked and, therefore, this case cannot be included in the report.

discrepancy. In the first disagreement the frog indicated pregnancy and the rabbit nonpregnancy. However, owing to the history and clinical findings, this patient was operated upon soon afterward with a pre-operative diagnosis of ectopic pregnancy. Upon laparotomy, an unruptured tubal pregnancy was discovered in the pelvis, the diagnosis of which was later confirmed in the pathologic laboratory. In this instance, the frog was proved to be correct and the rabbit false.

The second disagreement also showed the frog reacting positively and the rabbit negatively. In this case, both tests were repeated one week later using a second urine specimen. This time both animals were positive. Again, this would seem to indicate that the frog was more sensitive than the rabbit in diagnosing early pregnancy.

It is thus evident from our short series of cases that the frog is a very sensitive indicator of early pregnancy. While we do not suggest any necessity for replacing the Friedman test or the Asehheim-Zondek test in the usual pregnancy diagnosis, there would appear to be a distinct advantage in using the *Xenopus* test in very early or ectopic pregnancies, or where rapid diagnosis is desirable.

TABLE II. ADVANTAGES OF "FROG TEST"

		XENOPUS	A-Z (MICE)	FRIEDMAN (RABBIT)
1	Rapidity	4-18 hr.	96 hr.	36-48 hr.
2	Simplicity	No operation	Requires operation	Requires operation
3	Economy	16 cents per frog	5 mice cost a dollar	One rabbit, \$1.50
4	Maintenance	Simple	Feeding and cleaning problem	Space occupying
5	Technique	Single injection	40 injections	One or two injections
6	Ease of injection	Subcutaneous	Multiple injections	Intravenous
7	Practicability	Can be used over and over again	Animals killed	Rabbit usually killed
8	Special precautions	None	Age and weight	Isolation
9	End reaction	Simple observation of eggs in water	Search for ovaries in five animals	Search for ovaries

TECHNIQUE

Frog Maintenance.—Our basic method of keeping the frogs entails the use of two 12-gallon aquaria for each ten frogs. One tank is used as a "rest" tank in which the animals recuperate for four weeks after receiving an injection, and the other tank is the "active" tank from

which animals ready for use are taken. The water in the tanks is kept at about a three inch level from the bottom. The frogs are fed small strips of beef heart, liver, and garden worms (if available) twice each week. Tank water should be changed to fresh water of the same temperature if the tank develops an odor.

For the actual tests, standard two-gallon tanks are used. These may be stacked one above the other for convenience in making a number of tests simultaneously. Half-inch wire mesh should be bent to form a platform about one inch from the bottom of each test tank to prevent the frog from devouring its extruded eggs. A set-up "test" tank should contain about three inches of water and should be kept covered with a glass plate, allowing for the passage of air. The water in all the tanks should be of the same temperature and the room for housing and testing should be bright and airy with little variation in temperature.



Fig. 1.—A positive reaction, showing hundreds of extruded eggs.

After each test it is advisable to burn off any contaminating eggs from the wire platform with a Bunsen burner, since occasionally some eggs adhere to the wire and may conflict with the results in the following test.

Concentration of Urine.—Although whole urine may be used, Crev and others suggest a simple concentration which can be performed in half an hour or less and which favors the more rapid deposition of eggs. The technique which we used follows: Eighty cubic centimeters of morning urine is acidified with glacial acetic acid until acid to litmus. Then 160 c.c. of acetone is added to the urine, causing a precipitation of proteins and hormones from the urine. The contents are thoroughly mixed and allowed to stand for fifteen minutes and then centrifuged. The supernatant fluid is discarded and the precipitate washed twice with 20 c.c. of ether. The precipitate is allowed to dry. Two cubic centi-

meters of distilled water are added to the dry precipitate and thoroughly stirred and then poured into a small centrifuge tube. Centrifuging again brings down excess protein while the hormone is soluble in the 2 c.c. of water. Just prior to injection the clear supernatant fluid is decanted and adjusted with 10 per cent sulfosalicylic acid to a pH of 5.5 by means of nitrazine paper (Squibb). One cubic centimeter of the concentrate is used for the injection while the remaining cubic centi-



Fig. 2.—Injecting the *Xenopus*.



Fig. 3.—Dissection showing position of needle during injection.

meter is reserved for use in case of recheck, or a second frog may be injected immediately. By means of this simple concentration each cubic centimeter of the final concentrate is equivalent to 40 c.c. of whole urine.

Method of Injection.—Care as well as experience is required when injecting into the lymph sac of the toad. To miss the lymph sac and puncture the lung usually means death of the frog. The animal is injected by means of a long, flexible needle into the dorsal lymph sac. This lymph sac is reached by thrusting the needle superficially into the left thigh muscle, and then directing the point of the needle steadily

upwards to the middorsal line (Fig. 2). Throughout its course, the needle should be seen clearly just beneath the skin. A firm gentle thrust carries it through connective tissue into the lymph sac. Great care must be exercised to keep the point of the needle extending upward and away from the animal to avoid puncturing the left lung (Fig. 3).

Reading the Test.—After the animal has been injected with the urine concentrate, it is placed in the waiting test tank and watched. Positive extrusion of eggs may be seen as early as four hours after injection. The tests were read at eight to twelve hours, when reactions were usually complete. If after eighteen hours no eggs are visible in the tank, the test may be considered negative and the animal placed in the "rest" tank for use again in a few weeks.

*Advantages of the *Xenopus*.*—As will be noted from Table II the frog is at least as accurate as the rabbit. The test is simpler, more rapid, and more economical since the frogs can be used over and over again. The frogs are easier to handle, care for, and maintain than either mice or rabbits. The frogs require small amounts of foods and few feedings, the space and care are minimal, and the test requires only one subcutaneous injection of 1 c.c. of urine concentrate.

Other Hormone Reactions.—It has been demonstrated experimentally⁴ that progesterone, testosterone, and adrenal cortical extracts in large doses will cause ovulation in *Xenopus laevis*, but since these hormones do not occur in normal urines in quantities sufficient to produce the reaction, the idea of conflicting results may be dismissed. However, the potential value of the frog as a biologic assay animal for anterior pituitary-like hormones should not be overlooked.

SUMMARY

A series of 53 suspected cases of early pregnancy tested with *Xenopus laevis* ("frog" test) and checked with the Friedman (rabbit) test showed 100 per cent accuracy in the frog. It is suggested that the "frog" test, because of its high degree of accuracy and the rapidity of reaction, four to eighteen hours, may be used where speedy pregnancy diagnosis is imperative. Other advantages of the frog test are discussed.

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ACCESSORY APPARATUS TO ASSIST IN PROPER POSTURING OF THE PELVIC INLET

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PELVIORADIOGRAPHY as advocated by Caldwell and Moloy requires, first, a set of stereoradiographs of the pelvic inlet with the patient in the supine posture. Proper posturing of the patient when taking stereoradiographs of the pelvic inlet is essential for later interpretation and typing of the pelvis.

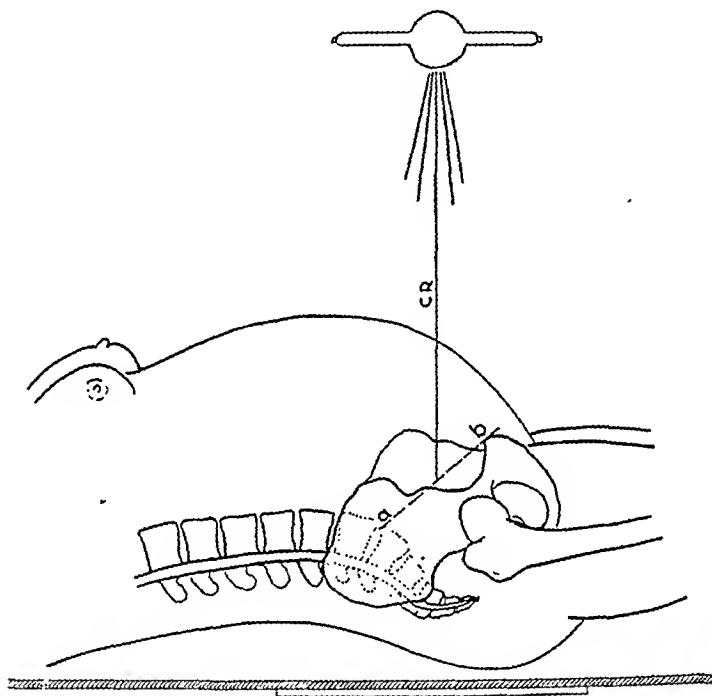


Fig. 1.—Plane of inlet *a-b* without pad.

It may be observed from Fig. 1 that with the patient in the supine position the plane of the pelvic inlet is not parallel to the plane of the film. In order that the pelvis may be typed with a minimum of difficulty, some device is necessary for tilting the plane of the inlet to bring it parallel to the plane of the film.

Caldwell and Moloy advocated the use of a lumbosacral pad as illustrated in Fig. 2, to place the pelvic inlet in its proper relation to the plane of the film.

This means of tilting the inlet has been practiced in the Department of Roentgenology of the Margaret Hague Maternity Hospital for some time. During this time I had occasion to notice a great deal of discomfort to the patient when the heavy pad was placed under the curve of the lower spine.

With a view to eliminating this discomfort and at the same time maintaining my standard technique, I had built an angle block with a 20 degree caudal slope. The patient rests supine on this block with a pillow underneath the head and shoulders without discomfort. The block must be so placed so the lower border of the block is pressing lightly against the superior margin of the patient's buttocks. Speed in handling our

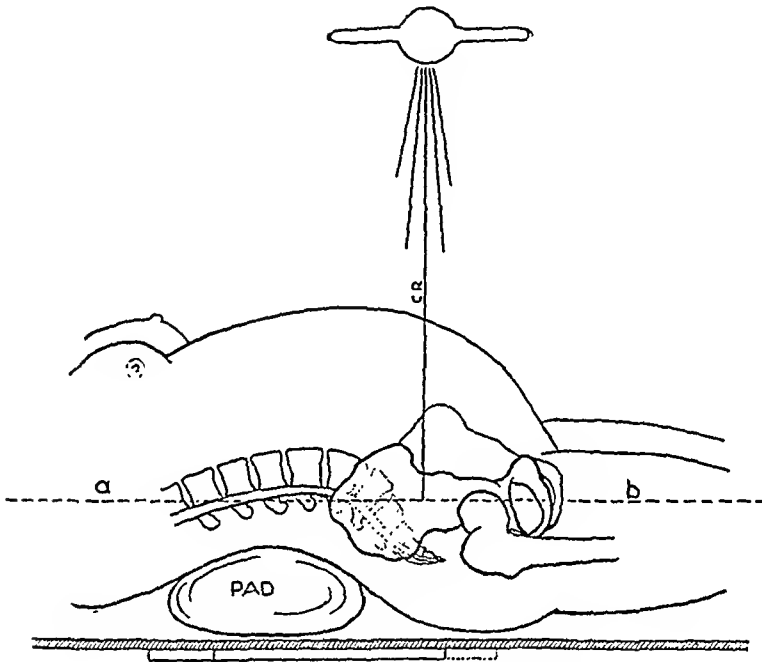


Fig. 2.—Plane of inlet *a-b* with pad.

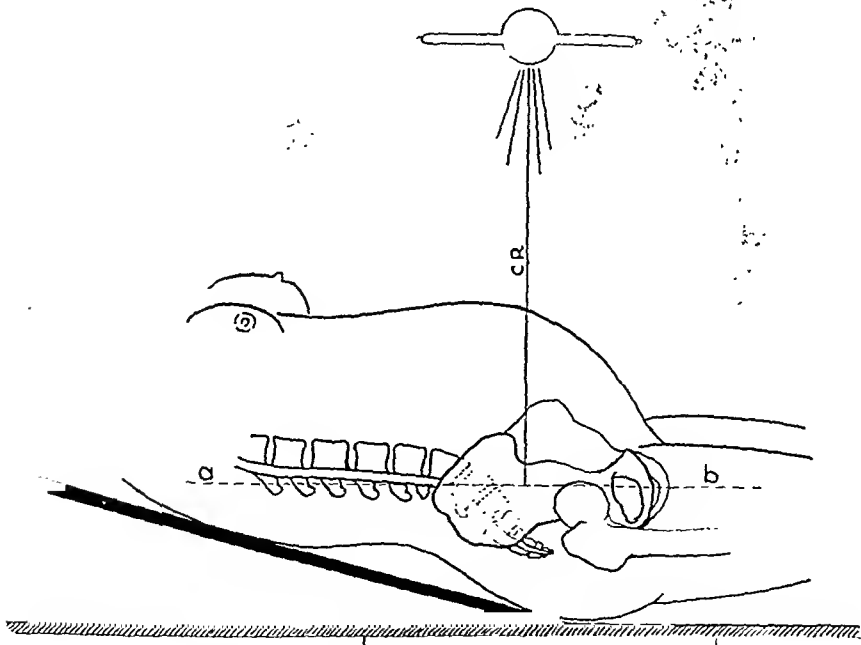


Fig. 3.—Plane of inlet with angle block *a-b*.

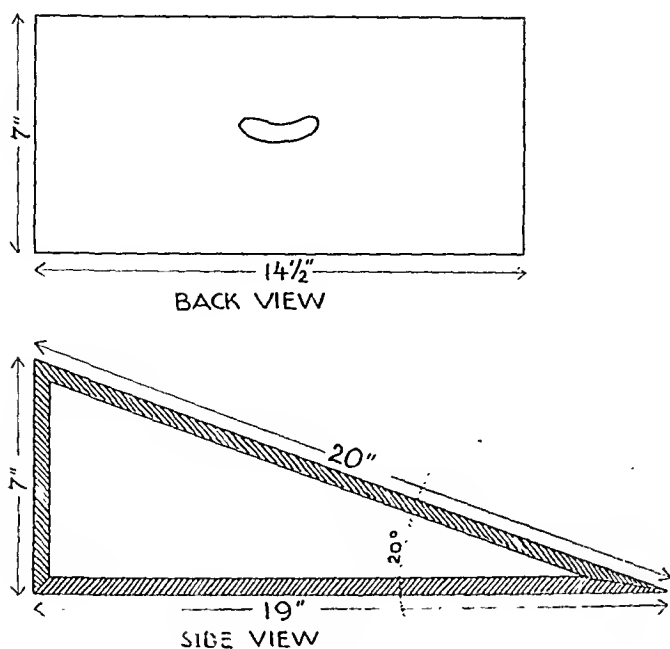


Fig. 4.—Diagram of angle block.

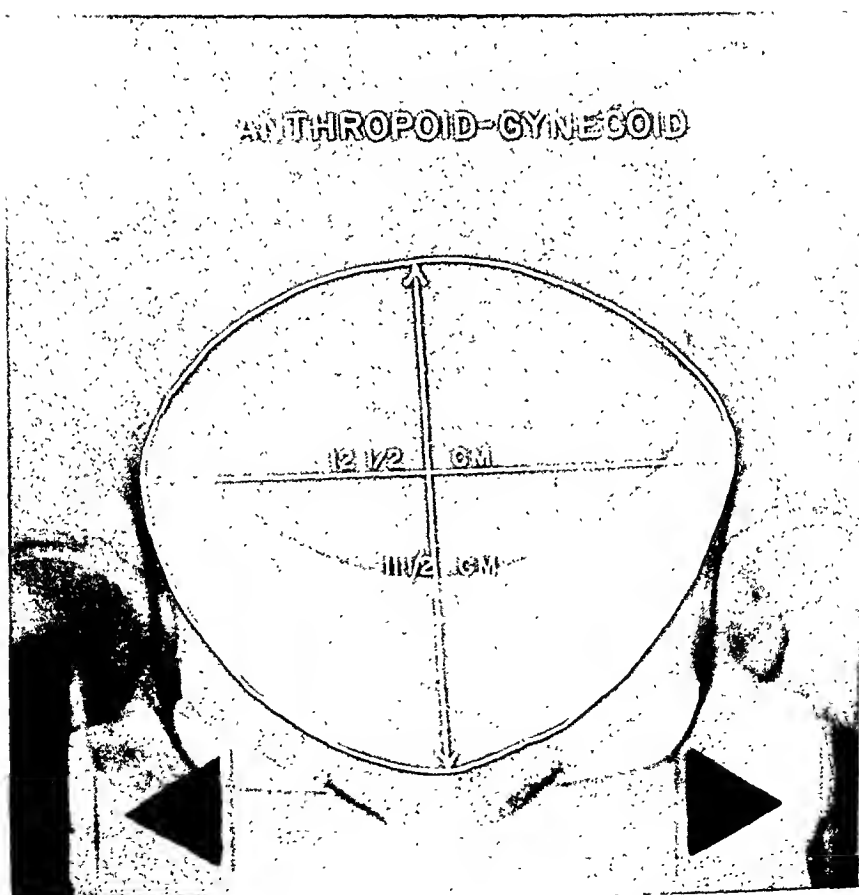


Fig. 5.—Radiograph taken with use of lumbosacral pad.

work is facilitated by the induced cooperation of the patient who is at ease in this posture. The plane of the inlet and film are unchanged.

The angle block is similar to the various angle blocks used for projections of the accessory sinuses or mastoids, being only a trifle larger. It may be used for such additional projections as gastrointestinal tract when unorthodox specified projections are requested or for projections of the thorax and might be considered useful in locating apical lesions with the patient recumbent.

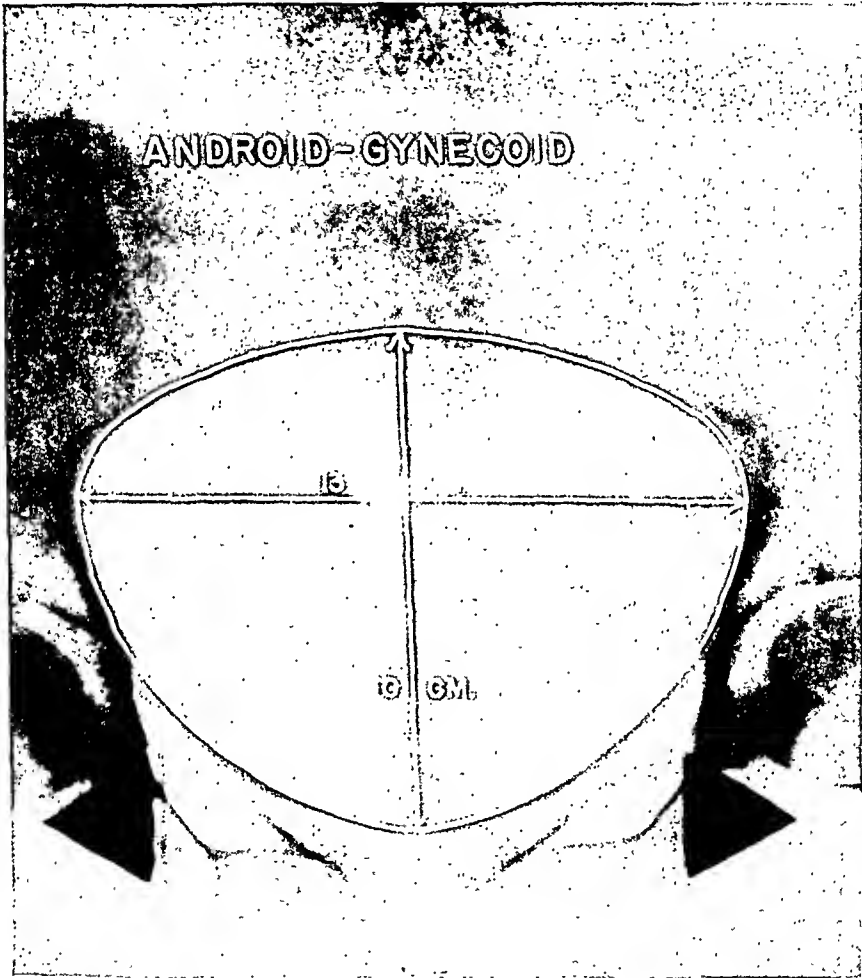


Fig. 6.—Radiograph taken with use of angle block.

As is the case in all angle blocks used for various projections, nails should be eliminated, strong but lightweight wood of good quality should be used. An opening of sufficient size to permit entrance of the hand is placed in the rear of the block to permit rapid and easy handling.

I wish to express my gratitude to Dr. S. A. Cosgrove, Medical Director and to Dr. H. J. Perlberg, director Department of Roentgenology for their review of this paper.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

THE PROBLEM OF MATERNAL MORTALITY STUDIES IN THE SMALLER HOSPITALS

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DURING the past ten years the question of maternal mortality has been given widespread publicity and study. That this campaign, sponsored by lay groups and the profession, has done much to lower mortality rates is unquestioned. Statistics are being compiled by individuals and study groups which report marked reductions in certain causative factors of maternal mortality and point out other factors where further reductions can be expected.

The Pennsylvania State Maternal Mortality Committee, through its various committees, has done a monumental and worthwhile task in gathering together statewide statistics as to the cause of death in childbirth. Groups have been organized in the various larger cities to study maternal deaths and to determine the preventable factor in each case and assign the blame for the tragedy to whomever or whatever factor is responsible. If these study groups are worth while in Philadelphia, New York, and Chicago, why are they not just as worthwhile in smaller communities? The answer is they are, but that certain factors mitigate against their success in the small town.

In the first place, in small towns there are few and sometimes not any practitioners who are devoting all their time to obstetrics. It is too much to expect a busy practitioner, who is doing obstetrics along with a general practice, to be exercised over maternal mortality. He will read about it but promptly consign the article to the waste basket as a fad and continue to do things as he has done them for the past twenty years.

In the second place, in the average 200 bed hospital, the obstetric staff is composed of one full-time obstetrician, or none, with several busy practitioners who do general practice plus a large obstetric practice. Interest in a group discussion of fatalities in this hospital is difficult to arouse and difficult to maintain. The meetings are poorly attended and the physicians will not speak their minds because of the fear of arousing the ire of their fellow practitioners. In other words, the physicians in a small town know each other too well to give or take honest criticism.

In the third place, the average small hospital has a series of deliveries too small to embrace all the complications, and cases suitable for study occur too infrequently to maintain interest in a regular meeting. The study is sporadic and soon dies a natural death. Maternal mortality is a subject that must be kept continually before the profession if any good is to come of an organized study group.

What is the solution to the problem in our smaller communities? We think that we have solved these difficulties in part by our method of procedure. In this vicinity, we have four hospitals located in three cities all within an 18-mile radius. Hospital A has 800 deliveries a year; Hospital B has 750; Hospital C has 650; and Hospital D 700. This is a combined total of 2,900, which is a fair-sized number for statistical study and among which more complications and fatalities are bound to occur. Three years ago we organized the Lehigh Valley Obstetrical Society which was comprised of the Obstetrical Staffs of the four hospitals as charter members. The organization was very simple. We agreed to meet at the four hospitals in rotation every three months with the hospital staff at which the meeting was being held to be host to the gathering. It was agreed that each hospital staff would bring to the meeting the chart of each fatality that had occurred in that hospital since the last meeting. An effort was to be made to obtain data on deaths that occurred in the home from a puerperal cause, but these are surprisingly infrequent in that these patients are usually brought to the hospital when they become ill or the emergency becomes great enough. The attending physician is notified that his case is coming up for discussion and invited to attend the meeting. In most instances, he or she appears but is not named in the discussion so that very few of the group know whose case is being studied. The case is presented by a disinterested person and discussed from all angles to elicit a preventable factor and, if possible, to assign the responsibility for the fatality. The discussion is frank. If criticism of treatment or method of procedure is meted out in a particular case no one becomes angry because the audience is present to profit by its mistakes. We have had some very heated discussions, but I have yet to see a physician take offense at justified criticism. If the meeting is hampered by too few cases to discuss, the host then introduces a topic for discussion which has been agreed upon at the previous meeting. These topics are obstetric complications, such as disproportion, hemorrhage, etc., and charts are produced to illustrate treatment of these complications, diagnosis and treatment being stressed. Frequently a member of the group is permitted to display his hobby, and we have had some interesting obstetric photography, favorite techniques, etc.

The beginning was slow but the growth has been healthy. Our first meeting was attended by eight interested physicians. Since then our attendance has grown and now averages 40 to 50. Nursing groups now attend regularly, particularly nurses of the obstetric departments from the various hospitals in the group and the visiting nurses of the towns in which the hospitals are situated. That they are interested and benefit by the discussion is evidenced by the regularity and increasing number of the attendance.

We think that the program has made most of the members more careful in their work and judgment in complications. A number of the men have told me that when presented with a problem in diagnosis or a choice of procedure, they remember the discussion on similar cases and are doubly careful to prevent the particular case in which they are working from becoming the subject of discussion at the next meeting. Or if they are so unfortunate as to have to present their case, they will have done nothing or omitted no procedure for which they could be criticized. Thus a friendly rivalry has been growing between the staffs of the component hospitals to have the best record since the preceding

meeting. Surprisingly enough, the thought of presenting a fatality at one of our meetings is in the back of our conscience when we are treating complications or contemplating an operative procedure. This makes us "indication-conscious," if I may coin a phrase, and we are doubly careful to err on the side of caution and conservatism, all of which will benefit the patient and make for better obstetrics.

Another fact has emerged from our meetings. When we first discussed cases, we ended our discussion with the reading of the death certificate. It was evident that there were attempts by the profession to "cover up" a death; in other words, to so word the final diagnosis that it would look as if the patient had died from a complication which was unrelated to the puerperal state. Criticism of this fact has been so frank and open that it is very seldom we find the "cover up" attempted. Now we "call a spade a spade" and if a patient dies of sepsis or peritonitis we call it just that and resolve to be more careful in the future as to our techniques and indicated procedures.

We are attempting to standardize our charts and procedures in the four hospitals so that in the future we will have larger case series from which to obtain statistical data.

The whole setup has untold possibilities. We hope to work out inter-hospital consultation service so that one hospital may have the benefit of the wisdom and judgment of three other hospital staffs in problem cases. We have had interhospital inspection of the maternity departments in which the host staff proudly displayed new equipment and building additions. Criticisms have been invited and welcomed.

We have not as yet touched morbidity or fetal mortality in our discussions but plans are being formulated to take care of these phases of our work as soon as our charts are completely standardized.

We think that we have, in part, solved the problem of maternal mortality discussion in the smaller hospitals. The ever-widening scope of our meetings has created new, and renewed old, interest in a pertinent problem. The setup is applicable in most small towns where there are hospitals within comfortable driving distance of each other. The purpose of this paper is to bring our method of procedure to the attention of the profession with the hope that it will be tried in other small communities.

MATERNITY HOME CARE FOR UNMARRIED MOTHERS

A STUDY of the special institutions caring for unmarried mothers before and after the birth of their babies was included by the Children's Bureau as part of a social-statistics project during the years 1937 through 1940. Monthly reports were obtained from 84 institutions located in 37 urban areas; all maternity homes within each area were included. (*The Child*, Nos. 3 and 4, 1941.)

The number of institutions in these areas varied from one to five and the number of women under care in the total area maintained an average of approximately 2,000. During 1940 the total number of women cared for in these homes was 9,942, ranging from 62 in Akron to 981 in Chicago.

The number of women admitted to the homes per 100,000 population varied from 8 in Baltimore to 193 in Syracuse. In the middle half the rates were between 25 and 67. (The total birth rate for the country as a whole was 17.1 per 1,000 in 1937 with a reported illegitimate rate of

40.2 per 1,000 live births, making a total reported illegitimate rate of 68 per 100,000 total population.)

Those who were local residents of the reporting areas varied from 13 per cent in Sioux City to 90 per cent in Houston. The relatively low proportion of resident women cared for in some areas indicates that the service is available to a geographic area which is statewide and in some instances even wider.

The average length of stay of each individual was 94 days with a range of from 14 days in Syracuse to 174 days in Atlanta and Richmond.

Of the 84 maternity homes included in this series, 19 were under the auspices of Catholic agencies, 18 were affiliated with the National Florence Crittenton Mission, and 21 were under the auspices of other religious denominations, nonsectarian boards and a public agency. (It is significant that in only one instance was the institution tax supported.)

Attention should be drawn to the fact that maternity home care is only one part of the service provided for unmarried mothers in a well-organized plan for their needs and lacking in this study is information on case work services provided to unmarried mothers by family-welfare, child-caring and health agencies. Studies recently conducted in several areas have revealed serious gaps in the service available and have made it apparent that there is insufficient knowledge of the extent of the problem of unmarried parenthood in these areas.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

MENTAL DISORDERS ASSOCIATED WITH CHILDBEARING

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(From the Department of Neurology and Psychiatry, Indiana University School of Medicine)

HISTORICAL

THE fact that mental disorder may complicate childbearing is an ancient observation. Hippocrates,¹ Celsus, Galen and Soranus^{71,73} recorded instances of post-partum psychoses. Hippocrates believed that these were due either to suppressed lochial discharges, a diversion of milk from the breast to the brain, or to the influx of blood to the breasts and his theories of etiology persisted for centuries. Esquirol² believed that the mental disorder possibly could be due either to milk deposits in the brain or the sex of the child. In 1847, James Maedonald⁴ reported a series of cases of "puerperal insanity" and maintained that a special form of insanity could be distinguished. He did not believe that suppression of milk had etiologic significance and pointed out that autopsies of such cases failed to reveal milk in the cranium or abdominal cavity. Marcé,⁷ in 1858, was the first to challenge the traditional views and maintained that there was nothing specific about puerperal mental disorders and these did not differ from psychoses occurring in nonpuerperal women of the same age. Unfortunately, his contributions were disregarded for fifty years and physicians continued to believe that a specific type of "puerperal insanity" existed.

The literature⁸⁻²⁵ between 1860 and 1900 is filled with case reports of "puerperal insanity" which were further subdivided into "insanity of pregnancy," "puerperal insanity," and "insanity of lactation." This nomenclature was supposedly based on etiologic considerations. Thus, the psychoses of gestation were due to anemia, albuminuria, physical exhaustion, domestic unhappiness and fear of childbirth; those of puerperium due to pain, shock, infection, and hemorrhage and those of lactation due to exhaustion, anemia, and depletion by prolonged nursing. The predisposing cause for all types was primarily neuropathic heredity, but poor mental and moral training and illegitimate pregnancy were also considered significant. No attempt was made to classify the type of mental disorder except on the basis of the phase of childbearing in which it occurred. Since several types of mental disorder, each with its own prognosis, may occur in any phase of childbearing, it is obvious that their statistical tables were useless for prognosis. Inasmuch as no such nosologic entity as "puerperal insanity" exists, there appears to be even less reason for such terms as "gestational," "puerperal," and "lactational" insanity.

From 1900 to 1915, various authors²⁶⁻⁴⁴ demonstrated that no specific mental disorder occurred in relation to childbearing. The literature of this period is largely concerned with the re-classification of these puerperal mental complications into the regular scheme of psychiatric diagnosis.

INCIDENCE

The exact incidence of mental disorders associated with childbearing is unknown. Numerous attempts have been made^{10, 21, 26, 28, 43, 44} to ascertain their rate of occurrence but reports differ greatly. Estimations of the number of women admitted to mental hospitals because of puerperal mental disorder have varied from 3.1 per cent to 21.6 per cent. The majority of statistics indicates that about 8 per cent of female admissions to mental hospitals are because of mental illness associated with childbearing. This figure does not give the real incidence since many women have a mild, transitory psychosis or toxic delirium from which they recover at home or in a general hospital and are therefore not included in the mental hospital statistics.

Attempts have been made to approach this problem of incidence from another standpoint, namely, the frequency of puerperal mental disease in relation to the total number of deliveries. The findings of different observers have been in total disagreement and have varied from 1 psychosis in 80 deliveries¹⁰ to 1 in 2,000.³⁴ This wide discrepancy has never been satisfactorily explained although various authors have believed that the illegitimacy rate of the community, the economic level of the patients, social unrest and war, the physical health standards of the group and many other factors might explain the wide variation. In short, the relative frequency of mental disorders and the number of deliveries is unknown and all existing figures have failed to include those cases developing insidiously after convalescence from delivery. The accepted rate is 1 complicating mental disorder in 400 deliveries, but this figure has little except tradition to support it.

THE NATURE AND CAUSES OF PUERPERAL MENTAL DISORDERS

Mental disorders, rather than constituting disease entities, are better understood as inferior and maladapted patterns of reaction designed to meet biologic, social, and personal problems confronting the individual. Different individuals possess variable quantities of psychic reserves with which to meet various social, physical, and psychologic stresses. If these threats to mental integrity are minimal or the psychic resistance and reserves are optimal, the individual remains "normal." However, some individuals have a paucity of psychic assets or are subjected to an overwhelming load and are unable to cope with the situation in the usual and expected manner. They respond to stress with behavior patterns that are poorly adapted for efficient social adjustment and are therefore termed "abnormal." The exact type of abnormal pattern of reaction will depend on many factors, some constitutional in nature and others which are determined by the individual's training, experience, habitual modes of thinking, and emotional problems and conflicts.

From a psychiatric viewpoint, childbearing constitutes a difficult life situation which imposes physical, physiologic, psychologic, and social stresses upon the pregnant woman. To remain "normal" she must react to these in the usual and accepted manner and not allow underlying

emotional problems and conflicts to appear in symbolic forms and abnormal behavior which are unrestrained by the demands of reality. Pregnancy is often a test of the stability of the personality and even an uneventful gestation imposes heavy burdens on the patient's psychic organization. Any disturbing factor, whether a mental conflict, toxemia or social unrest, will lessen the patient's capacity to control her emotional difficulties and constitutional tendencies to some form of mental disorder.

The physical and physiologic disturbances of the average gestation are myriad in number, every part of the maternal organism reacting in the complete metabolic reorganization of pregnancy. While in the midst of this physiologic reorganization, the pregnant woman is subjected to other disturbances which further exhaust her psychic and physical reserves. During the late months of gestation, she has difficulty in securing sufficient rest. Usually she has headache and nagging pains which are irritating and exhausting. Mild toxic states occur which disturb the patient's equilibrium without producing obvious clinical manifestations. At the time of delivery, tremendous demands are made on the patient's capacity for physical readjustment to meet the shock and exhaustion of labor, hemorrhage and multiple thromboses, laceration and infection, and toxicity from hypnotics and anesthetics. Following delivery, another major metabolic readjustment must be made including involution of the reproductive organs and initiation of lactation. Further physical depletion occurs when the mother assumes the care of the child and resumes her household duties. However, none of these factors acts as a specific cause of mental disorder. These are the predisposing causes which operate by so reducing the clarity of consciousness and the powers of repression and self-control that underlying conflicts, problems, and constitutional tendencies are expressed in pathologic behavior and thought. In view of these facts, it is interesting to note that nearly all observers have reported that only a small proportion of their patients have had a history or evidence of unusual physical depletion. It would appear that physical causes are not of major significance except in cases of toxic delirium.

The possibility that endocrine changes of pregnancy might play an important etiologic role has received serious consideration.^{81, 90, 95, 98} At the present time, there is little definite data regarding the relationship between the hormonal tides and psychologic reactions and objective studies¹⁰⁶ have only recently been undertaken. In addition, Karnosh and Hope⁹⁸ made prolactin estimations and quantitative estrin studies in ten cases of post-partum psychoses and found low normal values which did not differ appreciably from those of nonpsychotic puerperal women. The widespread therapeutic use of hormone preparations in mental disorders has only added confusion to the problem of the role of the endocrine glands in the production of psychiatric disorders. Unfortunately, a few publications have appeared which credited one or another hormone preparation with miraculous specific therapeutic action in "puerperal insanity," but evidence was not presented to show that these results were not due to suggestion or to the coincidental remission of a self-limited psychosis. For the present, it may be admitted that marked changes occur in the endocrine functions during pregnancy, but there is no conclusive evidence to show that this is of specific significance in the production of puerperal mental disorders.

Nearly all writers have agreed that psychologic factors are the most important in the etiology of puerperal mental disorders. Childbearing has a psychic significance^{66, 78, 83, 100} as well as physiologic aspects. This important epoch calls forth many emotional attitudes, the nature of which will depend upon the patient's personality and patterns of thought and feeling. Every woman must undergo a mental reorganization in her pregnancy in reaction to this new life situation. The period of gestation has been known traditionally as a time of feminine irritability, emotional instability, and unpredictability. Some of this may be in reaction to underlying emotional problems but physical discomfort, nagging aches and inconveniences will also contribute. Individuals differ in their ability to tolerate discomfort and the less stable react with exaggerated emotional responses. Of greater importance, however, is the patient's reaction to childbearing as a significant milestone in her life. It will mean that her period of carefree youth is ended and adult responsibilities must now be assumed. For some women the pregnancy may represent the cementing of an unsatisfactory marriage and will mean that she is now morally and economically bound to a shiftless, unstable husband. Selfish women resent the fact that they will no longer be pampered but now must share the husband's love and attention with a newborn rival. Vain and self-centered patients who are in need of constant adulation often become emotionally disturbed by the fear that pregnancy may cost them their beauty. Physiologic capacity for pregnancy is not always accompanied by a corresponding psychologic maturity necessary to meet the emotional problems incurred by childbearing.

In some patients it is not unusual to find mental conflict over moral issues concerning pregnancy because it represents the culmination of their sexual life. Many women of strict background and training have been taught that the sexual aspects of life are disgusting and degrading even in marriage. One who has been taught that pregnancy is the supreme punishment for sin and sexual misbehavior will have difficulty in accepting gestation without deep feelings of guilt. Thus, some women have uncontrollable emotions of shame and embarrassment during pregnancy because of the feeling that others regard them as guilty of wrongdoing. In some, powerful conscious and unconscious sexual conflicts are revived and cause severe emotional unrest. These considerations suggest that patients impregnated extramaritally would be especially prone to emotional conflicts over sin but, paradoxically, most writers report that such moral issues are more common in married women. The sexual life of patients with puerperal mental disorders has been studied,^{71, 72, 85, 107} and it has been found that 60 per cent of puerperal manic-depressive and schizophrenic women were frigid in marriage, but the same proportion is reported^{85, 107} in nonpuerperal psychotic women. It appears that a large percentage of these women have been unable to reach an adult, mature sexual level. However, instead of this operating as a specific etiologic factor, it is more probable that this only represents an index of their emotional immaturity and incomplete personality development which renders them more liable to mental disturbances.

Another psychologic factor of importance is the attitude of anxiety and fear of some patients approaching delivery. Some women have a personality which is poorly organized to tolerate pain and adversity. Many have been sheltered from the realities of life and in pregnancy

find themselves confronted with the first problem that their parents cannot solve for them. Frightened by old wives' tales and having no experience in fortitude, they approach term with terror and despair and only a minor event is necessary to precipitate a major mental crisis.

Economic and social factors also play an important part in shaping the attitude of a pregnant woman. She is in a particularly helpless condition and not able to meet sudden social and economic dislocations. During the Napoleonic wars, the occurrence rate of puerperal psychoses increased rapidly,^{2, 3} and this rise was out of proportion to the general trend of female admissions. More recently, Karnosh and Hope⁹⁸ have demonstrated the same disproportionate increase during the depression. Economic insecurity and social unrest add to the difficulties of a pregnant woman, and she must face the fact that her gestation will end with a new problem of caring for another child.

In the majority of cases it is impossible to demonstrate a major, dramatic psychologic trauma which has served as the exciting cause of a puerperal mental disorder. Rather, the minor nagging worries and difficulties seem to have a cumulative effect, especially in multiparas. Some women find their life monotonous, meaningless, and punctuated only by frequent episodes of childbearing. For them, another pregnancy may represent an intolerable life situation in spite of previous easy and uncomplicated deliveries.

In short, puerperal mental disorders are due primarily to psychologic causes but social, physical, and toxic factors play a part in the release of underlying reaction patterns. Whether or not a mental disorder will appear in association with childbearing will depend upon a personal equation which is different for each patient. It might be formulated: Is the patient's psychic reserve (hereditary constitution, training, personal psychologic organization) sufficient to resist the factors producing mental disorder (toxicity, endocrine imbalance, psychologic conflicts engendered by pregnancy)? Thus, a patient of poor personality organization may become mentally ill in spite of excellent physical health and few apparent socioeconomic-psychic problems, while another individual of more sthenic personality structure passes mentally unscathed through the most adverse and complicated circumstances of childbearing.

Finally, it is necessary to differentiate between mental disorders complicating childbearing and pregnancy complicating a psychotic episode. Certain patients have recurrent episodes of mental illness during which pregnancy occurs in a coincidental relationship. Others conceive as a result of indiscretions or heightened eroticism due to mental disorder. For example, an unmarried woman was diagnosed as having a puerperal mental disorder but investigation proved that the sexual relationship and conception occurred as a result of mental confusion associated with an advanced schizophrenic psychosis. The coincidental occurrence of pregnancy and mental illness does not establish childbearing as the prime etiologic factor.

TIME OF ONSET

Although no diagnostic or prognostic conclusions can be reached by ascertaining whether the complicating mental disorder began during pregnancy or during early or late puerperium, it is still of value for the obstetrician to know which periods are the most dangerous from the psychiatric standpoint. The literature (Table I) reveals consider-

TABLE I. TIME OF ONSET OF THE MENTAL DISORDER

AUTHOR	PREGNANCY PER CENT	PUERPERIUM PER CENT	POST-PUERPERAL PER CENT
Macdonald, ⁴ 1847	6.0	66.0	27.0
Hengst, ⁹ 1878	18.0	47.0	35.0
Ballantine, ³⁸ 1909	12.0	74.0	14.0
Sandy, ⁴⁰ 1913	15.0	28.0	57.0
Bear, ⁵⁵ 1921	20.0	63.0	17.0
Riggs, ⁵⁶ 1922	11.3	46.4	42.1
Armstrong-Jones, ⁵⁹ 1923	22.0	44.0	33.0
Bourne, ⁶² 1924	6.0	60.5	33.5
Cruickshank, ¹⁰⁹ 1940	16.0	84.0	32.0
Median and average estimates	14.0		

able disagreement concerning this point and this may be due to the different limits assigned to the puerperal period by various authors. One writer classifies all psychoses occurring within two or three months as "puerperal" while others designate any disorder after the lying-in period as "lactational." For this reason, the statistics supply only an estimate of the frequency of mental disorders in these various periods. An average of sample statistics throughout the years suggests the following frequency distribution: Pregnancy 14 per cent, early puerperal (the first 14 days post partum) 54 per cent, late puerperal 32 per cent. These figures have little claim to mathematical exactitude and have value only as indicators of the most vulnerable periods for the onset of mental disorders.

RELATIONSHIP BETWEEN MENTAL ILLNESS AND PARITY

There has been considerable disagreement whether mental illness is more prevalent in primiparas or multiparas, and many conflicting reports could be cited. This disparity is due to the practice of comparing the frequency of psychoses in the two groups without reference to the disproportion in the number of primiparous and multiparous pregnancies. Mental disorders of all types are probably slightly more frequent in multiparas, but the difference in the proportionate rate of occurrence in the two groups is not great.

DIAGNOSTIC CLASSIFICATION

The mental disorders associated with childbearing can be classified readily in the ordinary scheme of psychiatric diagnosis, inasmuch as they do not differ in symptomatology or prognosis. Table II records the frequency distribution of the various psychoses in series of cases reported by different authors. There is some variation in the percentages of each disorder but the figures are in general agreement. A median and average estimate suggests the following gross distribution of diagnoses: Manic-depressive psychosis 40 per cent; schizophrenia 20 per cent; delirium 28.5 per cent; psychoneurosis 6 per cent, psychosis with psychopathic personality 5 per cent. Other types of mental illness, such as general paresis and alcoholic psychoses, may occur but they are infrequent and only coincidental.

MANIC-DEPRESSIVE PSYCHOSES

Manic-depressive psychoses, especially those in the depressive phase, are the most common of the puerperal mental disorders. The ultimate

TABLE II. DISTRIBUTION OF TYPES OF MENTAL DISORDER

AUTHOR	MANIC- DEPRESSIVE PER CENT	SCHIZO- PHRENIA PER CENT	DELIRIUM PER CENT	PARANOID CONDI- TION PER CENT	EPILEPTIC PSYCHOSIS PER CENT	ALCOHOLIC PSYCHOSIS PER CENT	GENERAL PARESIS PER CENT	PSYCHOSIS WITH MENTAL DEFICIENCY PER CENT	PSYCHOSIS WITH PSYCHO- PATHIC PERSONALITY PER CENT	ACUTE TRANSI- TORY EXCITE- MENT PER CENT	PSYCHO- NEUROSIS PER CENT
Ballantine, ³⁸ 1909	24.5	35.0	26.6		2.1	1.4	2.8				5.6
Sandy, ⁴⁰ 1913	53.0	17.0	26.0	3.0 (1 case)							
Gregory, ⁴⁰ 1924	45.0	16.0	28.0		3.0	1.0 (1 case)		1 (1 case)		5	
Strecker, ⁶⁶ 1926	36.0	26.0	34.0				2.0				2.0
Kilpatrick and Tiebout, ¹¹⁰ 1926	49.0	13.0	34.0								4.0.
Smalldon, ¹⁰⁷ 1940	48.1	28.8	3.6	0.45 (1 case)					5.4		12.6
Cruickshank, ¹⁰⁹ 1940	33.0	26.0	38.0					1			1.0
This series (150 cases)	31.2	17.6	28.8		1.6		1.6		4.8		14.4
Median and average estimates	40.0	20.0	28.5	1.0					5.0		6.0

cause of this disorder is unknown but various psychologic, biochemical, and endocrinologic causes have been suggested. Although final etiologic conclusions cannot be reached, it is agreed that this psychosis is most likely to occur in people of a certain personality pattern termed the "syntonic temperament." Individuals of this type direct their energies and interests into the outside world rather than inwardly into their own mental life. Usually they are warm, tender, and sympathetic, responding emotionally in harmony with others and their environment. These individuals are often lively, energetic and socially active although some, because of shyness and lack of aggressiveness, give the impression of timidity and withdrawal. The whole group oscillate between the poles of warm, infectious gaiety and unobtrusive, taciturn somberness. Under the stress and pressure of psychologic conflicts or physiologic changes, it is possible that the underlying cyclic emotional swing may be so widened in amplitude that it constitutes obvious mental disorder. In the cases under consideration, pregnancy with its associated problems supplies the extra strain. Whether the patient's reaction will be manic or depressive in nature depends on unknown factors, but it has been suggested that unconscious personal problems, situational setting, and habitual modes of response decide this issue.

Once the manic-depressive reaction pattern is established it tends to recur when the patient is again under psychologic or physiologic stress. Thus, the initial attack may occur in association with childbearing, and repeated psychotic episodes appear in subsequent gestations. Cases have been reported in which twelve manic-depressive reactions ensued in as many pregnancies, the patient remaining mentally well in the interpuerperal intervals. On the other hand, although the syndrome may first appear in association with pregnancy, it may assume an independent existence and further attacks occur without reference to childbearing. Finally, the patient who already has an established, recurrent manic-depressive cycle is likely to have an attack during the puerperium, the pregnancy acting as a nonspecific stressful situation. In some cases, the gestation may appear to be an important etiologic factor; in others, it seems to be merely a coincidence.

MANIC REACTIONS

Manic reactions are infrequent during gestation. During this period an occasional hypomanic episode may be observed but a full-blown manic reaction rarely occurs unless the predisposition is marked or the patient has had previous attacks.

The most usual time of onset is seven to fourteen days post partum. During pregnancy there are frequently premonitory signs such as unusual nervousness and tension, flightiness or apprehension. The onset is usually abrupt after one or two days of prodromal excitement, garrulity and restlessness, although a short period of depression may precede the manic outburst. The clinical picture is characterized by extreme excitement, rapid flow of thought, grandiose ideas, and motor overactivity. Often there is considerable confusion and uneasiness suggesting a toxic factor, but this usually disappears after a few days, leaving a relatively pure manic reaction. Actual states of toxicity may be engendered by the overactivity and diminished fluid and food intake, thus superimposing delirious reactions upon the underlying mania.

CASE 1.—A married woman, aged 33 years, para iii, gravida iv, was admitted to the hospital because of uncontrolled restlessness, talkativeness, and bizarre

behavior. She was in the seventh month of gestation, her mental symptoms beginning during the fifth month. At this time she became highly elated, talked constantly in a flighty manner and expressed grandiose ideas concerning her ability, beauty, and desirability. She gave away her children's clothing, made many foolish, expensive purchases, and ran away from home on several occasions. Before admission she suspected her husband of infidelity and thought that he was not interested in the home. There was no basis for these suspicions, and they appeared to be projections of her own attitudes.

Physical examination revealed a well-developed, well-nourished woman without evidence of organic disease. All laboratory studies were consistently negative. Obstetric examination revealed a normal pregnancy. She delivered a normal child at term without complications.

During her hospital residence the patient was elated, overactive, and talked constantly with a flight of ideas, usually expressing dissatisfaction with her marital situation. Often she sarcastically referred to her husband, ridiculing his intelligence, appearance, cultural standards, and earning ability. She projected her own conflicts upon him, stating that he did not care for her, he wanted to be with other people, and, "He dislikes me because I get pregnant so often and he made insulting references about the source of my pregnancy." At all times she was correctly oriented and clear in comprehension. A diagnosis was made of: Manic-depressive psychosis, manic phase, third attack.

The family history was negative for mental abnormality. The patient's history revealed no serious illnesses. She had completed a common school education and was an intelligent woman who felt confined by the limitations of a small town. Her personality pattern was described as sociable, aggressive, and ambitious. At the age of 24 years she married a plodding, mediocre individual and delivered her first child within one year. Ten days after this delivery, she became restless and talkative, referred to her husband as an enemy and expressed grandiose delusions concerning herself and her future prospects. At times she tore off her clothing, destroyed household furnishings, screamed and laughed loudly, and was disheveled in appearance. This behavior continued for five weeks and eventuated in recovery. No unusual mental manifestations were apparent during the second or third pregnancies. Two years before the present admission she had measles and influenza, and a second manic attack, four weeks in duration, complicated this illness.

The present episode subsided after delivery but reappeared as soon as she returned home. She became noisy and overactive and refused to live with her husband, at times threatening to kill him. This attack lasted one year and was so severe that state hospital care was necessary. After apparent recovery, she was informed of her impending discharge from the hospital in the care of her husband and another short manic episode occurred immediately. Following parole from the hospital, she separated from her husband and children and established a home in a large city. She apparently remained healthy and happy for twelve years until another manic attack necessitated return to a mental hospital.

It is usually difficult to manage these patients, and they create a problem on the obstetric ward because of their noisiness, intractability, and inability to cooperate in the nursing regime. Often they become exhausted, malnourished and dehydrated, and incur dangerous infections. It is imperative to maintain a high caloric intake and adequate fluid balance by mechanical feeding or intravenous infusions if necessary and to secure sufficient rest by means of sedatives. As soon as the obstetric condition permits, the patient should be transferred to a psychiatric hospital for continued care.

DEPRESSIVE REACTIONS

Although depressive reactions do not present such startling and dramatic symptoms as the manic phase, they constitute an equal or greater hazard to the life of both the mother and child. Often the

family and physician overlook or minimize post-partum depressive states, especially when there has been an obvious precipitating sad event, and regard the patient's behavior as "natural grief" and are surprised to find that this reaction has quietly progressed to a deep depression.

The time of onset is from a few days to a few weeks after delivery; only a small minority of cases occur ante partum. Occasionally, the depressive reaction begins rather abruptly with initial symptoms of confusion, perplexity, and apprehension and then shifts to an obvious mental depression. In other cases the onset is insidious, progressing almost imperceptibly from a mild discouragement to a deep depressive state. Coincidental or precipitating toxie reactions may be noted in the early phases, but these soon disappear as the physical condition improves, disclosing the major underlying depressive trend.

The clinical picture is characterized by physical and mental lethargy, retardation of thought and action, sadness and self-accusations of unworthiness and wrongdoing. The outstanding feature is the emotional depression and the sense of futility. This leads to a loss of appetite or unwillingness to take nourishment and fluids, and secondary malnutrition, dehydration, and toxicity often occur. The clinical course of such a patient is shown in the following case:

CASE 2.—A married woman, aged 22 years, para ii, was admitted to the hospital three months after her last delivery because of mental depression, ideas of great unworthiness and physical failure. Her obstetrician stated that her health had been excellent throughout gestation. Delivery was spontaneous following five hours' labor and no complications occurred. She was delighted with the child and was in excellent spirits until the sixth day when she suddenly began to cry, fearing that she was to die. Her physical health continued to be excellent, and she was discharged from the obstetric ward on the eleventh day. The mental depression deepened and was accompanied by a slow physical failure due to refusal to eat or otherwise attend to her bodily needs. She lost 20 pounds in weight.

Physical examination revealed a poorly nourished woman who appeared to be acutely ill. The skin was flushed and greasy and an acneform eruption covered the face. The eyelids and lips were swollen. No definite physical disorder could be detected. Laboratory studies were negative.

The patient's facial expression was one of complete dejection and hopelessness. She talked slowly in a subdued, monotonous voice, expressing ideas of great unworthiness and sin. Usually she maintained that she was "no good," that the pregnancy had been a mistake, that the baby "wasn't all right," and that she had sinned by bringing him into the world. She wanted to die, yet was afraid that she would. Her sin had made the whole world suffer, especially her husband and children. The patient stated that her mind was flooded with such feelings of sadness and despair that it was impossible to think of anything except the enormity of her sins. Occasionally, voices taunted or questioned her about wrongdoing.

The patient's physical condition improved slowly. Soon she was able to be placed in a chair where she sat motionless, her head bowed, completely disinterested in everything except her own sad thoughts. Improvement in the mental condition occurred slowly during the next two months; the ideas of unworthiness gradually disappeared, and she again became interested in return to her husband and children. The total duration of her mental illness was six months and she was eventually discharged as recovered. The diagnosis was: Manic-depressive psychosis, depressed phase, first attack.

The family history was negative for mental abnormality except that her father was heavily alcoholic and irresponsible. The patient's history revealed no serious illnesses or accidents. In personality she was considered to be shy, sociable, fun-loving, and occasionally high tempered. At the age of 15 years she left home to work in a large city, and while there had been intimate with at least three men and had contracted syphilis. She returned home and married without mentioning her

previous experiences. The marital adjustment was fairly good but the economic adjustment was always precarious, the family receiving Welfare aid for the past two years. During the last pregnancy, the patient had quarreled with the husband because of his absences from home and his inability to support her.

After recovery the patient stated that on the sixth day post partum, she had experienced an intense anxiety and fear that she would die. She believed that this idea had been suggested by hearing the howling of a dog. Immediately afterward she heard voices discussing her premarital sexual promiscuity and syphilitic infection, and once she thought she saw the devil pass by her door. Later she imagined hearing her husband's voice asking about her misconduct, and she actually confessed to him, hoping to relieve herself of the awful feelings of guilt. This brought no relief and she continued to ruminate constantly about her sins and the possible syphilitic infection of her children. These guilt feelings became more severe when she recalled that she had allowed pregnancy to occur in order to force her husband to stay home nights with her. She stated that during the early months of her mental illness she often thought of destroying herself and the children to avoid the horrible fate that awaited all of them.

It is of paramount importance that the depressive state be recognized early so that suitable treatment and precautions may be instituted. The physical health of these patients declines rapidly and mechanical feeding or intravenous infusions should be used if the patient is unable or unwilling to take sufficient nourishment and fluids. Often these patients are unable to sleep at night and occupy themselves with horrible thoughts; in these cases sedation should be employed to supply necessary rest and prevent exhaustion. Elimination by bowel is usually impaired and cleansing enemas should be administered regularly. Inasmuch as she will be unable to nurse the child, necessary attention should be given to the breasts. As soon as the obstetric condition permits, the patient should be transferred to a suitable psychiatric hospital.

The greatest hazard is the constant danger of suicide and/or infanticide. These patients often believe that their condition is hopeless, that they and the children are doomed to everlasting suffering and that death is preferable to their mutual prospect. Suicide may be accomplished with the most meager apparatus and, therefore, everything of lethal potentiality must be removed from the room, the windows strongly screened and constant nursing supervision maintained. The child should not be allowed in the room and under no circumstances should the mother be alone with the baby. The possibility of suicide and infanticide in depressed patients cannot be overemphasized, since it is in this group of cases that self-destruction and child murder are most likely to occur.^{20, 69, 88, 89}

The prognosis of puerperal manic-depressive psychoses is usually quite good. If this is the first attack the patient almost invariably recovers after a few months. Only a few develop permanent persecutory syndromes. If there have been previous attacks, the present disorder will probably be longer and more severe than the preceding episodes. Further pregnancies may or may not be complicated by repeated attacks, depending upon associated factors.

SCHIZOPHRENIA

Schizophrenia or dementia praecox comprises about 20 per cent of psychoses associated with childbearing. This pathologic reaction pattern appears most frequently in individuals of a certain psychologic constitution designated as the schizoid personality. A schizoid person is characteristically cold and reserved, living within himself and avoid-

ing close contact with his fellows. Often shy and timid, he finds solace in daydreams and attempts to shield himself from emotional situations. These individuals are sensitive and easily hurt but hide their feelings beneath a reserved, unemotional exterior. They often have deep attachments binding them to their parents and experience considerable difficulty in transferring their affection to others and attaining an adult, mature, emotional relationship. The schizoid person is a perfectly normal type but schizophrenia may develop in individuals of this personality pattern who are not able to meet the demands of reality. The exact etiology of this disorder is unknown but apparently it represents a withdrawal from reality into a childlike world of fantasy, symbolism, and disconnected, fragmented thought. The withdrawal may be so slow and imperceptible that it is difficult to determine when it began, but usually the final break is ushered in by an acute excited episode. In this phase the patient entertains bizarre delusions, hears imaginary voices, and his mental processes are confused and disorganized. This acute episode occasionally terminates in complete or partial recovery but more usually progresses to advanced mental deterioration. Most psychiatrists believe that this pathological reaction pattern occurs because of the individual's inability to meet the exigent demands of reality which, in the present cases, are represented by the problems and vicissitudes of childbearing.

The majority of puerperal schizophrenics have a typical history of aloofness and introversion. They have preferred to remain emotionally bound to their parents and have had few, if any, love affairs of any consequence. Often they married their first and only suitor after a long, lukewarm courtship and many were so reluctant to marry that familial pressure was necessary. Their reaction to marriage was unenthusiastic and the majority were sexually unresponsive, finding marital intimacies aesthetically distasteful. While the general marital adjustment may be fairly satisfactory, it is apparent that the wife has not attained a psychological sexual maturity and a full emotional relationship with her husband.

During gestation these patients are often morose, irritable, and flighty, and these symptoms may progress to a schizophrenic episode before term. Usually these manifestations are disregarded by the physician and family and ascribed to the "nervousness of the pregnant woman." After delivery it is noted that at times the patient appears odd, preoccupied, and uncertain in her behavior and makes occasional illogical and meaningless remarks. Her attitude toward the husband and child is frequently that of disinterest or open antagonism. Often these peculiarities are not outstanding and the acute psychotic episode, which may appear a few days after delivery or be postponed for several weeks, is completely unexpected. The mental manifestations correspond to those usually seen in schizophrenia. In addition, frequently the patient openly expresses her dissatisfaction with her husband and symbolically reveals her attitude toward the child by fearing or dreaming that he has been lost, kidnapped, or killed, or by denying her marriage and pregnancy. The excitement and associated refusal of food and fluids may cause a febrile and toxic reaction which sometimes leads the physician into making an erroneous diagnosis of a primary toxic state with secondary delirium. The following case is fairly typical.

CASE 3.—A married woman, aged 21 years, para i, was admitted to the hospital because of violent, disturbed behavior. The mental symptoms began four days after delivery. Her health was excellent during gestation and the delivery was easy and

uncomplicated. On the fourth post-partum day she had an unexplained fever of 102° F. for three hours. She became irrational, saw snakes and rabbits in the room, and believed that poison had been placed in the food. The mental disorder continued without abatement until her admission three weeks after delivery. No further physical complications had occurred.

Physical examination revealed a well-developed, well-nourished woman who did not appear to be acutely ill. Physical, gynecologic, and laboratory examinations were negative for organic disorder.

The patient's facial expression was that of passivity and disinterest. There was no clouding of consciousness or memory disturbances. At times she appeared perplexed but more usually she was indifferent and apathetic. Her answers to questions were vague and inadequate, and she frequently stared blankly into space. Blocking and disorganization of ideas were apparent in her stream of thought. The most outstanding characteristic was the dulling of emotions, and she was quite indifferent to her surroundings and the possibility of returning home. She never asked about the baby except to say, "I wouldn't cry much if something happened to my husband or the baby." On another occasion she stated that if her husband were to die she would marry a much nicer man, although this statement was quite irrelevant to the topic under discussion. Occasionally she muttered vaguely to herself about losing her beautiful figure. Auditory hallucinations occurred constantly, and she was frequently found sitting quietly, vaguely fumbling with her hair and staring vacantly into space while listening to her schoolgirl friends whispering to her.

This apathetic state alternated with periods of disturbance. During these episodes she was quite unpredictable, often suddenly assaulting those about her without provocation. She suddenly struck a nurse saying, "Don't say that, I'm no Christ." Often she tore off her clothing, shouting that her body was cowlike or that a married man was trying to seduce her and her sister. On occasions she was found in sexual postures as if carrying out imaginary relations. During the most excited period she decorated her hair with bloody rags.

The family history of this patient was completely negative. In personality, she had been a quiet, solitary, shut-in type of individual who had few friends. She was self-willed and irritable and had moody episodes when faced with any difficulty. She married the first and only man with whom she had dates. Conception occurred within the first three months, much against the patient's wishes.

The patient's further course was that of rapid physical and mental decline. She lost 15 pounds in weight in two months in spite of tube feeding. She became untidy in appearance, silly and deteriorated in her behavior, and spent her time laughing and shouting in response to imaginary voices. This reaction pattern continued after transfer to a state hospital where she died eight years later of pulmonary tuberculosis. The diagnosis in both hospitals was: schizophrenia, hebephrenic type.

In the present series of cases a few of the patients had psychotic symptoms early in pregnancy; some became suspicious and perplexed just before term but the majority had an acute onset within ten days post partum. These schizophrenic patients were divisible into two main types. In the first group were those individuals whose first psychotic break was severe and permanent, necessitating state hospital care. The second included patients who had had a previous mild or severe schizophrenic episode from which they had made an incomplete recovery. They had been able to live in the community but were queer, eccentric, emotionally cold individuals who evinced little interest in their homes, husbands, or children. Each succeeding pregnancy caused a severe exacerbation of their chronic psychosis and added an increment to their mental disorder until finally state hospital care became necessary. These latter cases clearly demonstrated the danger of allowing further pregnancies to occur in a woman who has had a puerperal schizophrenic psychosis.

The diagnosis of schizophrenia implies a very serious prognosis and the majority of these patients progress to a severe mental deterioration. The chances of recovery are about 1 in 4 or 5 and even if apparent recovery occurs there will usually be some residuals (emotional blunting, eccentric behavior, marital maladjustment). However, when schizophrenia occurs in relation to childbirth, it appears to have a slightly better outlook than in ordinary cases. This may be due¹⁰⁷ to the fact that the majority of cases are of the catatonic type, which regularly has a better prognosis, or because the disorder is precipitated by a specific difficult life situation. It is not unusual to see a surprising improvement in severe cases of puerperal schizophrenia and a poor prognosis should be withheld until the patient is well-advanced in the chronic phase.

DELIRIOUS REACTIONS

The toxic-exhaustive delirious states constitute about 28.5 per cent of the puerperal psychoses. These cases were quite frequent before the present era of aseptic obstetrics and the older physicians, noting improvement in the psychosis some time after an abscess was evacuated or some other toxic or exhausted state had disappeared, concluded that all puerperal mental disorders had a similar toxic-exhaustive origin. Some few still hold to this concept and fail to recognize the human personality factor in the production of a mental illness. The fact that some individuals pass through the most severe types of intoxicating processes without the appearance of a psychosis suggests that a personal psychologic predisposition plays an important role. Actual investigation reveals that many of these delirious reactions occur in patients who are laboring under such severe psychologic stresses and conflicts or who have such unstable personality organization that any physiologic or emotional crisis precipitated a delirium. Many of the delirious patients in this series were recognized as unstable, maladjusted persons long before their pregnancy. The psychologic resistance to delirium is no less real than the physical immunity to infection.

The delirious reactions are usually precipitated by infections, toxemias, excessive hemorrhage, severe exhaustion, and metabolic intoxications which cause a clouding of consciousness, hallucinatory states, and the release of underlying conflicts in a symbolic form. The amount of toxicity and exhaustion necessary to produce a delirium will depend upon the personality organization and life situation of the individual patient. What may be a negligible toxicity in a happy, stable woman will be overwhelming to a patient whose ordinary life burden taxes her to the limit. In short, the mere presence of toxicity or exhaustion will not invariably cause a delirium but, instead, the toxic-exhaustive factors and the personality problems confronting the patient must be weighed against the individual's psychic resistance. Viewed in this light, the delirious patients in the present series could be divided into two groups:

1. *The Toxic Deliria.*—This reaction occurred most frequently in women of considerable stability who had shown an average ability to manage the problems of their lives. Many had had previous uncomplicated pregnancies. However, in the present pregnancy some severe toxic state had occurred with the subsequent appearance of delirium. Such an intoxication may occur at any time during gestation or the puerperium, but it is most commonly seen in the first three to five days post partum. The delirium usually immediately precedes or accompanies the physical manifestations but may appear several days after

the toxic state has been established. These patients present the physical picture^{46, 47, 49} of an acute toxic state with fever, dryness of the skin or sweating, and rapid wiry pulse. Mentally, the most outstanding features are unclearness and confusion with disorientation, memory disorders, wandering of thought, derangements of perception, vivid auditory and visual hallucinations, disturbances of comprehension, and even states of stupor. The emotional state is variable, some patients being fearful while others are apathetic. In some, the emotional changes are at times suggestive of a manic or depressive reaction, while others show occasional bizarre reactions of a schizophrenic or persecutory nature. While in this confused state, these patients usually discuss their personal problems either openly or in a symbolic manner.

During the acute psychosis, these patients present a difficult problem in management because of their excitement and overactivity. The fear induced by terrifying hallucinations and the state of disorientation may lead to efforts to escape their persecutors and tragic accidents and suicides have occurred when adequate supervision was not available. Practically all recover their previous mental status without psychotic residuals, but the duration of the illness is extremely variable. Some recover their mental health as soon as the toxic factor is removed; others remain confused for a few days or weeks, while a small percentage continue in a confused state for months before re-establishing mental equilibrium.

CASE 4.—A married woman, aged 21 years, a primipara at term, was admitted to the obstetrical ward because of recurrent vaginal bleeding. She soon went into labor and a healthy child was delivered by episiotomy and the low application of forceps. Examination of the placenta revealed old blood clots, showing that premature separation had occurred. Twenty-four hours after delivery she had a severe chill and the temperature was elevated to 104.5° F. and fluctuated about this level for the next nine days. The patient complained of low abdominal pain, and muscular rigidity was noted in this area; the lochial discharge became foul and profuse. As the pelvic inflammation subsided, it was possible to palpate a mass in the lower right abdominal quadrant. Hemocytologic studies revealed a profound secondary anemia and leucopenia; intrauterine culture revealed gram-positive diplococci but repeated blood cultures were negative.

Coincidental with the onset of the fever, the patient became confused and bewildered. She was terrified at finding clusters of spiders on the wall, black cats surrounding her bed, and white cats on the bedspread. Men of monstrous appearance pulled the covers off her, while tiny golden men, four inches in height, with a spike growing out of the tops of their heads, ran and dove at her, imbedding their heads in her flesh. Thick, red lips appeared on the wall and poured out a torrent of obscenity and discussed her personal life. A huge woman had massive feet planted in opposite corners of the room and babies kept emerging from the giant labia, falling on the bed of the patient who tried to dodge them. At times she would inspect her hands minutely in a perplexed manner to ascertain if any small animalcules were present.

The confusion and clouding of consciousness varied considerably and periods of complete lucidity and logical thought alternated with episodes of unrestrained fear, screaming, and violent efforts to defend herself or escape from her persecutors. At no time did she express any organized ideas of persecution. She had no idea of why these things were happening and could think of no one who would wish to harm her.

The patient was given general supportive treatment, oxytocics, blood transfusions, and sedation. The pelvic infection rapidly responded to treatment, and there was a simultaneous improvement in the mental condition. At the end of ten days, she was mentally clear and had insight into her previous condition. Discussions revealed

that she was an average middle-class woman who was happy and satisfied with her life and had no outstanding psychologic problems. She was discharged in excellent condition and has remained well.

2. *The Nontoxic Deliria*.—These are variously known in the psychiatric literature^{46, 47, 49, 50, 96} as "amentia syndrome," "symptomatic psychoses," "exhaustion psychoses," "confusional insanity," and "symptomatic confused states." The patients displaying this syndrome often have a history of psychopathic heredity, pre-existing mental instability, and exaggerated psychologic responses to slight toxicity or exhaustion. Although it is generally assumed that this reaction pattern is in response to anemia, severe exhaustion, or toxic-infectious factors, this belief cannot be substantiated in the majority of cases. Usually the history reveals a normal, uncomplicated delivery and careful examination fails to demonstrate physical depletion or intoxication. In many of these patients the evidence of toxicity or exhaustion is so negligible that the diagnosis rests entirely on the psychiatric findings.

This syndrome appears almost exclusively in the post-partum period and may begin in two different ways, but the subsequent reaction pattern is the same in both instances. One group of patients experience the above-mentioned acute toxic delirium which continues in an attenuated form long after the precipitating complication has disappeared. Sir James Simpson pithily described this sequence, "The morbid clockwork runs on long after the key that wound the spring is withdrawn." The second group usually have a gradual onset two or three weeks after delivery. The clinical picture of the syndrome suggests a diluted delirium. Again, the outstanding manifestation is confusion and clouding of consciousness, the patient behaving in a dazed and bewildered manner. At first, she seems to be somewhat toxic and physically ill but little or no confirmatory evidence can be adduced. Later, this aspect of physical illness disappears, unless reinforced by nutritional disturbances and dehydration, and only the mental manifestations remain. The bewildered patient acts as though she were in a dream from which she cannot awaken. Usually the emotional state is one of perplexed apathy but episodes of fear and panic occur in reaction to threatening imaginary voices and terrifying delusions. Mental processes are slowed and confused, the patient speaking infrequently in a flat, halting voice. Complete disorientation often occurs. The patient's personal conflicts gain expression in symbolic thought and behavior resembling the mental processes of a dream. In some cases marked manic-depressive or schizophrenic trends may occur and occasionally one of these types may crystallize out of the amorphous dream state.

The majority of patients are mentally ill for three to nine months but eventually complete recovery usually occurs. However, they are prone to recurrent episodes of delirium on the slightest provocation and always represent a poor psychologic risk for situations of stress. Those who do not regain mental health are usually incorrectly diagnosed cases of schizophrenia. Indeed, it is easy to undervalue the manic-depressive or schizophrenic symptoms in these patients and occasionally they are later observed in an unequivocal attack of one of these disorders. The patient who shows strong trend reactions in a delirium is a poor mental risk for future pregnancies.

(To be concluded in the February issue of the JOURNAL)

Editorial

Maternal Pulmonary Embolism by Amniotic Fluid

IN CONSIDERING the problem of inexplicable maternal death occurring during or shortly following labor, clinicians will welcome a new point of view provided by the pathologists Steiner and Lushbaugh,* of the University of Chicago. As a result of their study of eight women, these authors have described a new obstetric syndrome which they believe to be responsible for most, if not all, deaths heretofore variously ascribed to obstetric shock, idiopathic post-partum uterine atony with hemorrhage, acute pulmonary edema of pregnancy, and other obscure conditions. Clinically, the syndrome is characterized by shock. Predisposing factors are uterine tetany, over-size baby, multiparity and advancing age of the mother. The essential pathologic lesion is a widespread embolism of the small pulmonary arteries by amniotic debris, vernix caseosa and meconium. The clinical and pathologic picture can be reproduced in rabbits and dogs by the intravenous injection of the particulate matter found in human amniotic fluid. The frequency of fatal cases in obstetric practice is estimated to be about 1 in 8,000 confinements. The condition is believed by the authors to be the commonest cause of death during labor or in the first ten hours of the puerperium.

A question of major importance for clinicians in this interesting and stimulating new thesis is whether pulmonary embolism by amniotic fluid is capable, per se, of causing obstetric shock. The authors' animal experiments provide the only direct evidence on this point, since the data of their human case material show that every patient suffering from embolism also had post-partum hemorrhage or some other abnormality which might conceivably have accounted for her shock. Inasmuch as evidence of animal experiments in a question of this kind can be accepted only with reservations, it is earnestly to be hoped that further investigation may settle it. For, as the authors themselves state, the diagnosis of the embolism can be made only by the presence of shock, and by the absence of any adequate explanation for it; physical signs in the chest are minimal or absent. Because post-partum hemorrhage or other potential causes of shock are, however, uniformly present, considerable clinical acumen must be needed in making the diagnosis, and even more in withholding the giving of blood, which the authors feel is contraindicated in the treatment of this syndrome. Unless the primary question can be answered, therefore, there is danger lest an uncritical ac-

*Steiner, P. E., and Lushbaugh, C. C.: J. A. M. A. 117: 1245 and 1340, 1941.

ceptance of the new thesis may lead to the loss of lives that might otherwise be saved. Such premature acceptance, moreover, is likely to be encouraged rather than otherwise by the authors' statement that their syndrome is probably the commonest cause of death from obstetric shock. Such a conclusion can hardly be correct unless it is also true that a majority of such deaths occur among women bearing extraordinarily large fetuses. At least half of the fetuses in the authors' cases were of very unusual size.

Whether the new type of embolism be eventually confirmed as a major cause of obstetric shock or not, however, is less pertinent for the moment than the fact that Steiner and Lushbaugh have made a contribution for which all clinicians will be grateful. Not only are their ideas on maternal shock as stimulating as any that have been advanced in recent years, but their studies have been conducted with unusual care and completeness. As such, they deserve the earnest attention and study of all obstetricians.

CARL BACHMAN, M.D.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Obstetrics and Gynecology

*Obstetric Analgesia, Twilight Sleep, the Barbiturates in Labor*¹ is a large, elaborately assembled monograph by Juan Leon containing numerous colored charts. After detailing the foreign and Argentine literature, he discusses the pharmacology of the barbiturates. The study itself utilizes pentobarbital sodium (nembutal) alone (80 cases), with scopolamine (40 cases), with paraldehyde (40 cases), and with chloral (50 cases).

The action on the child was noticeable but less than that observed with opiates. Fetal mortality was nil. Complete analgesia and amnesia was 39.6 per cent, relative 49 per cent, failure 9.5 per cent. Maternal mortality none. This is a clear-cut, scientific study of childbirth in all its phases, presented in a fascinating way.

R. T. FRANK.

This well-known standard textbook for nurses, *Obstetrics for Nurses*² by DeLee and Carmon, appears in its twelfth edition. The authors state that they have noted the advances in the science and practice of obstetrics and have included in this edition a simplification of the treatment of the puerperium as well as the more complex and exacting system of prenatal care now in use. There is much new material for the public health nurse and the subject of cross-infection in hospitals has received due consideration.

An innovation is the inclusion of a teaching outline on obstetrics for nurses, in thirty lessons. The outline and suggestions for the lectures should be helpful to the many physicians who are concerned in nurses' education.

PHILIP F. WILLIAMS.

In *Die Tägliche Gynäkologische Sprechstunde*³ by Rodecurt, we have an interesting discussion of the common lesions of the pelvic organs, and their abnormal physiology, which forms the bulk of the clinical practice of gynecology. He begins with a chapter on the relationship and influence of the heart, gastrointestinal, renal, and other systems on pelvic pathology and abnormal physiology. The author regards the *Trichomonas vaginalis* as an etiologic factor in 88 per cent of all cases of leucorrhea; mechanical cleansing of the vagina is favored as the best treatment.

¹*Analgesia Obstetrica, el sueño Crepuscular Barbitúrico en el Parto.* By Juan Leon, Professor Adjunto de Clínica Obstétrica de la Facultad de Ciencias Médicas de Buenos Aires, etc. 574 pages, 169 illustrations. El Ateneo, Buenos Aires, 1941.

²*Obstetrics for Nurses.* By Joseph B. DeLee, M.D., Professor of Obstetrics and Gynecology, Emeritus, University of Chicago, etc., and Mabel C. Carmon, R.N., Chief Supervisor and Instructor in the Birth Rooms, Chicago Lying-In Hospital, etc. Twelfth edition, revised. 291 figures, 651 pages. W. B. Saunders Company, Philadelphia, 1941.

³*Die Tägliche Gynaekologische Sprechstunde.* Von Dr. M. Rodecurt, Frauenarzt. 308 Seiten, 3 Abbildungen. Georg Thieme, Leipzig, 1941.

Other features of trichomonas infestations, its ascent into the uterus and peritoneal cavity, such infestations in men and in very young children are described. The author makes no mention of the use of the sulfanilamide group in the treatment of gonorrhea in women. There is an excellent presentation of the pituitary-ovarian-uterine relationship in a chapter on abnormal bleeding; and this cycle is further elaborated in the chapter on insufficiencies of hormones. Presumably, the many proprietary drugs mentioned in this chapter are estrogen preparations. Rodecort says in a chapter on sterility that this condition in Germany is responsible for a 100,000 birth loss each year. There is a chapter discussing the neuralgic-neuritic-vegetative symptom complex, in which a multitude of remedies are suggested. There is a short and rather unusual chapter on the cosmetic aspect of gynecology. The book ends with a discussion of dietetics.

PHILIP F. WILLIAMS.

Endocrinology

Hoskins' *Endocrinology*⁴ is a well-written survey of the entire field of endocrinology designed to interest the biologist, psychologist, premedical student, the physician who desires a "non-too-technical" hormonology, as well as the intelligent general reader. Such a task is not easy. The author has not oversimplified, nor resorted to the blatant "journalese" to which some writers have descended.

In the main his exposition is clear-cut, well arranged, and really informative. From the view point of the general reader, it may prove too detailed and confusing; from that of the biologist, too sketchy, and yet its appeal will include a large number of readers.

A huge amount of well-documented information, covering the entire field, will be found in these pages, including some of the newest investigations. The personal views of the author, naturally, as they should, tinge the presentation in many ways. Here his wide knowledge of the literature and his personal experience in the laboratory enable him to evaluate the important high lights justly.

In the introduction he turneth away wrath by stating "In assembling the data, . . . only a part of the obligations thus incurred are indicated in the text and in the literature lists." Yet such names as that of Marine in connection with the mass prevention of colloid goiter and that of Zondek in the clarification of the function of the adenohypophysis, should not have been omitted. Numerous and well chosen illustrations illuminate the text.

R. T. FRANK.

The *Archives of the Clinic and Institute of Endocrinology at Montevideo*⁵ have been published in two large fascicles, the work extending from 1937 to 1940. The reviewer's work was much facilitated by the summaries in French, English or German which conclude many of the articles, but many of the subjects were of sufficient interest and importance to warrant his reading them in the original Spanish. An introduction by Fournier, the director of the Institute, gives a background and history of endocrinology. The subject matter covered in these Archives is huge and contained in more than sixty-five articles. Some of these have appeared in the South American medical journals; others are reported here for the first time.

⁴Endocrinology. By R. G. Hoskins, Ph.D., M.D., Director of Research, the Memorial Foundation for Neuro-Endocrine Research, Harvard Medical School. Illustrated, 388 pages. W. W. Norton & Company, New York, 1941.

⁵Archivos de la Clinica e Instituto de Endocrinologia. Director, Professor J. C. Mussio Fournier. Tomo I, Fasc. 1. and 2. (1937-1940). Imprenta "Rosgal." Montevideo, Calla Cerro Largo, 1941.

Many articles deal with changes in bone and other portions of the body, due to hypo- and hyperthyroidism, among which I mention the resistance to therapy, eventually developing in the pitting edema of myxedema, as well as the anginas associated with thyroid disturbances. Attention is called to the so-called pseudo-Froehlich syndrome which is merely of transient nature. Many articles deal strictly with the laboratory phases of endocrinology, including bio-assay methods for the gonadotropic factors, many experiments on the various sex hormones and the adrenal hormones, as well as changes in the technique of bio-assay and of the male sex hormone. Clinically, attention is drawn to the increase in metabolism frequently noted in the menopause. An important article deals with the adjuvant action of estrogens in the treatment of menopausal diabetics. A report on the activities of the clinic shows that nearly four thousand patients were treated in the course of three years at the Institute. All in all, this is a very important contribution to endocrinology.

R. T. FRANK.

*Office Endocrinology*⁶ by Robert B. Greenblatt is a small brochure, covering a number of particular procedures for office methods of treatment which the general practitioner might want to perform. The presentation is somewhat haphazard, apparently not following any definite arrangement. Such procedures as vaginal smears, suction curettage, and the application of the Friedman pregnancy test are well described. Just why the short chapter on "Embryologic and Histologic Considerations of the Ovary" and "The Nature of the So-Called Syneityoma" are included, is not apparent. The author appears to consider that the treatment of bleeding from the myomatous uterus should be controlled by testosterone, with which not all will agree.

R. T. FRANK.

Miscellaneous

Abdominal Surgery of Infancy and Childhood,⁷ by Ladd and Gross, represents a portrayal of the surgical experiences accumulated by the surgical staff of the Boston Childrens Hospital over a period of twenty-five years. The original stimulus from which this book has been developed was the extraordinarily high mortality rate in children as compared with adults. This, the authors believe, is due to certain types of infection and to the many congenital abnormalities which are seldom encountered in later life. As one might expect, a great deal of the text refers to congenital malformations or dysfunctions and to various forms of herniation. Various lesions of the genital tract of both girl and boy babies have been discussed at some length. In discussing neoplasms of the ovary, Ladd describes five cases of malignancy in the eight instances encountered in his institution. X-ray irradiation, he states, should not be used following malignancy in ovarian neoplasm in children. The inclusion of a discussion of vaginitis in a text on abdominal pregnancy seems somewhat irrelevant.

The book is amply illustrated. The pathology, symptoms, signs, and differential diagnosis are thoroughly interpreted, and the technique is set up in detail. One feels that this volume should be of value to those who must diagnose and treat children's diseases.

PHILIP F. WILLIAMS.

⁶*Office Endocrinology*. By Robert B. Greenblatt, B.A., M.D., C.M., Professor of Experimental Medicine, University of Georgia, School of Medicine. Published under the auspices of the University of Georgia, School of Medicine. Walton Printing Co., Augusta, Georgia, 1941.

⁷*Abdominal Surgery of Infancy and Childhood*. By William E. Ladd, Professor of Child Surgery at Harvard Medical School, etc., and Robert E. Gross, Associate in Surgery, Harvard Medical School, etc. 268 illustrations, 455 pages. W. B. Saunders Company, Philadelphia, 1941.

The authors of this book, *The Premature Infant*,⁸ have had some twenty years of experience in the care and study of premature infants at the Premature Station of Sarah Morris Hospital, Chicago. Their contributions to this field of infant care are of considerable importance, when one considers that about half of the deaths of infants during the first month of life in the state of Illinois are reported as being caused by prematurity. The value of this book lies in its practical approach to the medical and nursing care of the premature infant. The equipment necessary for the proper care of these infants either in the hospital or in the home, or for transportation from home to hospital is described. Since, as the authors stress, adequate nursing personnel and care are of major importance for the survival of the premature infant, the greatest value of this book can be found in its careful and detailed description of the nursing technique and the daily routine employed at the Sarah Morris Hospital.

Where adequate care for the premature infant is made available to the entire population, a considerable saving of lives will result. A city-wide plan, with the Cook County and the Sarah Morris Hospitals as centers, has been in effect in Chicago since 1934. Since that year the infant mortality per 1000 under one year of age has dropped from 47.7 in 1934 to 28.8 in 1940. During the same time, the premature mortality has dropped from 42.6 per cent in 1934 to 20.8 per cent in 1940.

SOL LONDE.

This new volume, *Operative Surgery*,⁹ is a treatise on the surgical treatment of abdominal diseases, to which there has been added a separate discussion of such related subjects as anesthesia, pre- and postoperative treatment, surgical technique, and blood transfusions. The material has been contributed by thirty-four authors, all eminent in their particular fields, and edited by F. W. Bancroft.

The subject is divided into twenty sections, of which fifteen deal directly with abdominal surgery. The first section, a general discussion of the various types of anesthesia as well as pre-anesthetic medication, has been prepared by six authors. Blalock's section on Pre- and Post-Operative Therapy discusses not only actual technical details, but brings out the methods of handling abnormal physiology due to either general conditions or local disturbances. This section should be of value to gynecologists as well as to the abdominal surgeons. In discussing blood transfusions, Stetson describes the methods of preserving blood as well as the various blood substitutes. This section is of considerable interest because of the development of these methods in surgery of the present war. Stevenson and Reid have made an outstanding contribution on the fundamental principles of surgical technique. For the young or occasional operator this section should be of great help. The various sections on the surgery of abdominal disease leaves no room for criticism. In addition to the special section on anesthesia and pre- and postoperative treatment, practically all specific sections contain the individual ideas of the various authors with regard to anesthesia and preoperative care. Under surgery of the spleen, Maes and Rives have discussed at length the physiology and disorders of function in order that the surgeon may have at his command the available knowledge regarding the conditions for which surgery of this organ may be indicated. The book closes with a section on Nutrition in Abdominal Conditions by Anthony Bassler. This is an excellent section.

⁸*The Premature Infant. Its Medical and Nursing Care.* By Julius H. Hess, Professor and Head of Department of Pediatrics, University of Illinois College of Medicine, etc., and Evelyn C. Lundeen, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital, Chicago. 309 pages, 74 illustrations. J. B. Lippincott Company, Philadelphia, 1941.

⁹*Operative Surgery, Including Anesthesia, Pre- and Postoperative Treatment, Surgical Technique, Blood Transfusion and Abdominal Surgery.* Edited by Frederic W. Bancroft, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, etc. 1102 pages, illustrated. D. Appleton-Century Co., New York, 1941.

This book is a splendid contribution. Because of the relationship between pelvic and abdominal lesions in their general aspects and not infrequent association, it might seem that it was almost a "must" text for the library of the gynecologic surgeon.

PHILIP F. WILLIAMS.

Ellinger presents the subject of *The Biologic Fundamentals of Radiation Therapy*¹⁰ in a well-balanced volume. The expansion of the therapeutic use of radiation should make this presentation of value not only to radiologists but to physicists and practitioners. Following an excellent consideration of the physical and biologic properties of radiation, the author refers to the action of radium on the various tissues and systems of the body.

In the second part of the book, he describes the corpuscular rays and in the third part the ultraviolet light, concluding with a discussion on radiation, biology, and therapy. His closing chapter is one of particular value, for here he discusses radiation injuries and their prevention.

Ellinger describes the effects of radiation upon the endocrine glands and makes an important point in that a fundamental difference exists between the effect on healthy and diseased organs. He states further that radiosensitivity and anatomic changes do not always go hand in hand. He regards the healthy pituitary as radioresistant to a very large degree. The pathologic pituitary, he states, reacts well to irradiation. Discussing the effects of radiation upon the ovary, he brings out very clearly reversible and irreversible reactions. There is an interesting description of the effects of radiation upon the course of pregnancy and the fetus, and this topic is brought up again in another chapter on the "Effects on the Progeny of Radiation." Further in the text he discusses the physics of ultraviolet light, and other light rays, and the treatment of diseased organs by light. The bibliography includes 1,110 items and must be regarded as unusually comprehensive. This is a very full and interesting presentation of the subject.

PHILIP F. WILLIAMS.

Biological Symposia,¹¹ edited by Jaques Cattell, in its Volume III, presents a source book of information on "Muscle." The introductory by the editor of this volume, Wallace O. Fenn, draws attention to the great interest presented by muscle for physiological, chemical, and physical research. The fifteen articles cover many phases of the subject, from study of function of a single fiber, through action potentials, innervation, conduction, metabolism, and diseases of muscles. The contributions are by authors well known in this field of research.

R. T. FRANK.

These two volumes conclude the system of *The Therapeutics of Internal Diseases*¹² edited by George Blumer. In Volume IV, "The Alimentary Tract and Its Appendages, The Genito-Urinary Tract, Hematic and Locomotor Systems," are discussed by fourteen authors. This is a comprehensive presentation, bringing out all

¹⁰*Radiation Therapy. Its Biologic Fundamentals.* By Friedrich Ellinger, M.D., Research Fellow, Radiotherapy Department, Montefiore Hospital, New York City. 79 figures in text, 360 pages. Nordemann Publishing Company, Inc., New York, 1941.

¹¹*Biological Symposia. Vol. III. Muscle.* Edited by Wallace O. Fenn, Professor of Physiology, School of Medicine, University of Rochester, N. Y. Illustrated, 370 pages. The Jaques Cattell Press, Lancaster, Pa., 1941.

¹²*The Therapeutics of Internal Diseases.* Supervising Editor: George Blumer, Clinical Professor of Medicine, Yale University School of Medicine, etc., Associate Editor: Albert J. Sullivan, Adjunct Clinical Professor of Medicine, George Washington and Georgetown Medical Schools, etc. Volume IV, 791 pages, and Volume V, 765 pages, both illustrated. D. Appleton-Century Co., New York, 1941.

the modern advances in these conditions, with excursions into such varied lines of therapy as vitamins, physiotherapy and psychotherapy.

The chapter on the "Treatment of the Diseases of the Rectum and Anus" will be of particular interest to the gynecologists and obstetricians, as such lesions are very frequently called to their attention. The same might be said for the diseases of the genitourinary tract. There is an excellent section on sterility in the male. Here, the author has been cautious in his recommendations of hormones or their synthetic substitutes, and stresses the need for avoiding an antihormone response.

Musselman of New Haven has written an excellent chapter on "The Nonoperative Treatment of Gynecologic Diseases," particularly the menopause. Especially valuable for the general practitioner is the discussion regarding the indication for operative intervention in pelvic disease. The quickening interest in obstetric circles regarding the classification of the hypertensive complex in late pregnancy should make a study of Mosenthal's section on Nephritis and Hypertension worth while.

The fifth and final volume represents the contributions of ten authors. Turner discusses the "Diseases of the Endocrine Glands." Valuable, from a practical point of view, is the list of the commercial preparations and their equivalent values in estrogen, progesterone, etc. He, too, cautions regarding antibody formation in the use of these preparations. It is not without interest that he omits all mention of x-ray therapy in hypofunctional states.

The Smiths offer an extremely well-developed and modern concept of the use of vitamins in therapy in medical practice. Particularly good in this section is the discussion of physiology of the various vitamins and of the subclinical deficiencies.

PHILIP F. WILLIAMS.

The enlarged scope of health education in many communities has created a demand for a book on unified health education programs.

This manual, *Community Organization for Health Education*,¹³ is a committee report of the American Public Health Association to the Public Health Education Section and the Health Officers Section. It discusses the need of community organization for health education, and advises a cooperative effort on the part of the health departments, school systems and private agencies for such work. Procedures are given which might be adopted by different combinations of agencies, and examples are shown how various communities and cities have followed the recommendations. While there are differences in the basic plans and functions of the various agencies, this manual brings out the facts and shows how the difficulties in the organization of almost any community to achieve the maximum health may be overcome.

PHILIP F. WILLIAMS.

The 1940 volume of the New York Academy of Medicine on medical lectures to the laity, *March of Medicine*,¹⁴ has as much interest for this reader as any of its predecessors. Dr. Solley in the Introduction tells of the great interest today of the general public in scientific matters and explains the necessity for interpretation of the fragmentary facts reported in the press. Myerson discusses the "Inheritance of Mental Disease." It is interesting to note his negative opinions on sterilization employed to counteract the lines of heredity in mental conditions. In his essay, "Ascent from Bedlam," Hutelings describes present-day care of mental disease. Perrin Long gives a fine story of the discovery and clinical application of the

¹³*Community Organization for Health Education. A Committee Report of the American Public Health Association. 120 pages. The Technology Press, Cambridge, Mass., 1941.*

¹⁴*The March of Medicine. New York Academy of Medicine Lectures to the Laity. 1940. Columbia University Press, New York, 1941.*

sulfanilamide group. Long states "never before has such progress been made in the treatment of infectious disease as we have witnessed in the last five years." Resnikoff in an easy style describes the blood dyscrasias, mechanisms of blood coagulation, and the fascinating story of transfusion. Thomas Rivers tells most entertainingly the story of viruses, yellow fever, influenza, and other virus diseases. The volume will probably prove as beguiling to the physician as to the laity for whom it was originally intended.

PHILIP F. WILLIAMS.

Dorland's *The American Illustrated Medical Dictionary* appears in its nineteenth edition.¹⁵ This well-known, standard volume contains more than two thousand additional words pertaining mainly to endocrinology, physical therapy, biochemistry, psychiatry, drugs, surgery, signs and symptoms of diseases. In spite of continued accretion, it still remains within the compass of convenient desk size.

R. T. FRANK.

*Tuberculosis and Psychoses*¹⁶ with especial reference to the etiology of "discordant psychoses" is a monograph by Melgar in which he deals with the association of dementia praecox and tuberculous infection. A most detailed presentation of the world literature covering modern concepts on the etiology of the disease, serology and bacteriology is given. A large number of case histories are abstracted. The treatment of thirty-six patients with "Solganal B," a proprietary gold salt, resulting in 22 per cent of remissions, is detailed.

R. T. FRANK.

*Complete Weight Reducer*¹⁷ is a volume arranged in dictionary form, covering a large number of topics which might be useful for reference, particularly by the laity, and save them from being unnecessarily exploited by charlatans who abound in the field.

R. T. FRANK.

¹⁵*The American Illustrated Medical Dictionary*. By W. A. Newman Dorland, M.D., F.A.C.S. Nineteenth edition, revised and enlarged, with 914 illustrations, including 269 portraits. 1647 pages. W. B. Saunders Company, Philadelphia, 1941.

¹⁶*Tuberculosis y Psicopatías*. By Dr. Ramon Melgar. 266 pages. Talleres Graficos "Gasparini," Buenos Aires.

¹⁷*Complete Weight Reducer*. By C. J. Gerling. Harvest House, New York, 1941.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Sterility

Williams, W. W.: *The Germ Plasm Factor of Sterility*, Urol. & Cutan. Rev. 44: 582, 1940.

In the opinion of the author many of the obscure cases of sterility are evidently due to germ plasm disease, and this presents considerable difficulty, both in the matter of recognition of definite pathology, and of possible underlying etiologic factors.

In the male, the examination of spermatozoa furnishes a rather direct method of appraising spermatie health. It indicates the performance probabilities of sperm populations but not necessarily the potentialities of individual germinal cells which deviate markedly from the pattern of the rest of the population.

In the female, the appraisal of germ plasm disease is less direct. Endometrial biopsies indicate whether or not an ovum has developed sufficiently to cause maturation of the follicle and subsequent lutein formation. It indicates the activity of the secretions elaborated by the follicle and the corpus luteum, but tells nothing of the fitness of the mature ovum for fertilization.

Often little or no attention is given to spermatie defects, the attempt being made to gauge spermatie health by motility reactions alone. In the author's experience the most dependable evidence of significant spermatie disease is usually derived from a study of stained semen smears. Normal fertile men rarely produce over 20 to 30 per cent abnormal spermatozoa, whereas with infertile men the presence of over 40 per cent structurally abnormal cells is a common feature. Pathologic spermatozoa are often highly motile. It happens that most males who are sterile because of germ plasm disease will deliver in each ejaculate (aside from the abnormal cells) millions of normal-appearing, active spermatozoa. Experience has shown that the normal-appearing cells occurring in markedly pathologic sperm populations are commonly incapable of fertilizing an ovum, in spite of their normal appearance and behavior.

A woman who has anovulatory menses is likely to be sterile whether the anovulation is or is not a constant factor. There is no more justification for assuming that ova are normal because they develop sufficiently to cause the elaboration of estrin, progesterone and the concomitant endometrial changes, than to assume that all normal-behaving spermatozoa are always functionally capable of impregnating an ovum.

Unless woman is more efficient than animals in the development of healthy ova, and unless there exists in woman a marked difference in the relationship of normal ovogenesis to the estrual cycle and the concomitant changes, then we must assume that a much larger ratio than commonly supposed of so-called functional sterility, is actually the direct result of abnormal female germ plasm. Add to this the sterility of male germ plasm origin, and a problem of considerable magnitude is presented. Lesser abnormalities of the ovum and sperm may be difficult or impossible to demonstrate by any type of known laboratory test. The effect of the union of two such cells with only slightly diminished vitality may, however, be clinically as important as an outstanding defect of a single gamete.

Indications of germ plasm pathology are frequently observed in spontaneous abortions where blighting of the fertilized ovum and abnormalities of the fetus are common features. It is a common clinical observation in spontaneous abortions that the fetus cannot be found. Spontaneous abortions, as anovulatory menses, are more common with women of low fertility, those with irregular menses, and those approaching the menopause.

J. P. GREENHILL.

McClellan, R. H.: Human Sterility. Analysis of a Series of 400 Specimens of Spermatic Fluid, Pennsylvania M. J. 43: 1582, 1940.

The group study of sterility is the most logical approach and it should be systematic and complete, including both partners. A simplified but adequate technique for the laboratory examination of semen is outlined by the author.

A properly obtained specimen in relation to continence and method of obtaining it is of significant importance. It is emphasized that the finding of mere motility in the ejaculation does not always mean a normal specimen nor a potent male. Motility lasting sufficient time for the transport of the spermatozoa to the ovum is necessary for fertilization of the ovum, and in an adequate study of semen the duration of motility and activity of the spermatozoa should be investigated.

A study of the morphology by differential stain and count is a necessary part of an adequate assay of the semen, as more than 25 to 30 per cent of abnormal forms indicate at least temporary sterility for the male. A single though complete examination may be misleading, and it is urged that repeated examinations of specimens, obtained under as nearly ideal conditions as possible, be made. In an analysis of 400 consecutive specimens of semen from partners in sterile marriages, it was found that a large portion of the males (54 per cent) have abnormal semen and therefore, are to this extent responsible for the sterility.

J. P. GREENHILL.

Pryde, John: A Contribution to the Study of Human Fertility, Brit. M. J. 1: 12, 1941.

The author is of the opinion that there exists within the human intermenstrual cycle a limited period of fertility. To support this view he gives data abstracted from complete records of sexual activity kept by two pairs of young married partners. The first pair had 126 and the second 450 uncontracepted acts throughout 33 and 61 consecutive intermenstrual cycles respectively. These were distributed so that none fell between the tenth and thirteenth day of the cycles. No pregnancies occurred. Following this, pregnancy immediately resulted in both cases when the first uncontracepted acts occurred within the tenth to the thirteenth day of the cycle. The author believes that a general investigation along such lines, with couples who would keep accurate day to day records, would substantiate his findings of the existence of a limited period of fertility in the intermenstrual period.

FRED L. ADAIR AND W. H. PHILLIPS.

Lamar, J. K., Shettles, L. B., and Delfs, Eleanor: Cyclic Penetrability of Human Cervical Mucus to Spermatozoa in Vitro, Am. J. Physiology 129: 234, 1940.

A new method of studying penetration of cervical mucus by spermatozoa in vitro includes the use of microtubes and barrier-marker bubble. This method is considered better than slide-cover glass preparations because it prevents undiscoverable mechanical mixing of mucus and semen and drying of the preparation, and because it can be used to study penetration quantitatively and also to study longevity of the spermatozoa in the mucus.

Results of this method confirmed the "in vivo and in vitro" findings of Seguy and Vimeau, namely, that there is a cyclic production of a glairy, translucent

cervical mucus at about midcycle, which renders the cervix temporarily penetrable for spermatozoa. Roughly, the spread of this phase in this study was from day 9 through 19, but for any one cycle this period may be restricted to about four days. Indications are that menstrual discharge is penetrable by spermatozoa, but the mucus of the phase between menstruation and the midcycle is relatively impenetrable, and that of the phase between midcycle and the subsequent menstruation is impenetrable.

Correlated with the midcycle peak in penetrability is the peak in freedom from leucocytes, the peak in pH (except during the menstrual flow), the peak in the amount of mucus secreted, and the height of conditions favoring greatest longevity of spermatozoa in the mucus. It may well be that the actual viscosity of the mucus encountered by spermatozoa is lowest at the midcycle. It is suggested that both low pH and large number of cells in the "secretory phase" of the menstrual cycle may be caused, at least in part, by the low rate of secretion of the mucus.

An investigation of the cervical mucus over the cycle, by the "in vitro" method, is suggested in cases of otherwise unexplained sterility. A field of usefulness for artificial insemination may be developed in sterilities due to a persistent impenetrable cervical mucus.

J. P. GREENHILL.

Brunner, E.K.: An Experiment in Temporary Immunization Against Pregnancy, *Human Fertility* 6: 10, 1941.

The author used a phospholipid antigen prepared from sperm masses obtained from young bulls. The antigen, and the antigen plus cevitamic acid were injected into groups of female rabbits. None refused to copulate and no immunity to pregnancy resulted.

R. J. WEISSMAN.

Brown, R. L., and Gamble, C. J.: Comparative Spermicidal Powers of 15 Commercial Contraceptives, *Human Fertility* 6: 1, 1941.

The authors describe their technique of determining the spermicidal time of jelly type contraceptives in vitro. Thirteen of the marketed products show variations in spermicidal time from 2 to 348 minutes.

R. J. WEISSMAN.

White, M. D.: The Effect of Follicular Hormone on Non-Patent Fallopian Tubes, *Brit. M. J.* 1: 342, 1940.

White gave courses of five estradiol benzoate injections of 50,000 I.B.U. each at five-day intervals to 9 patients whose Fallopian tubes were nonpatent and 4 patients in whom the tubes were only slightly patent.

Five days after completion of the injections, the tubes were patent in 5 of the 9 women showing previous nonpatency, 4 having good tubal contractions. Of these, one of the women was five months pregnant at the time of the report and two others had had their first menstrual periods delayed two weeks following the treatment which the author interprets as early miscarriages.

Of the 4 patients showing patency only at high pressures, 3 became patent at lower pressures and one of these now has good tubal contractions.

The author reiterates Clauberg's theory that the tubal hyperemia produced by estrin stimulation softens the tubes so that where fine adhesions are present which obliterate the lumen, further instillations of lipiodal or carbon dioxide insufflation may break them down and so effect patency.

FRED L. ADAIR AND RAY YOUNG.

Leinzinger, E.: Dangers and Injuries by Contrast Filling of the Uterus and Their Prevention, München. med. Wehnschr. 87: 1023, 1940.

Leinzinger discusses the important advances made by hysterosalpingography in the diagnosis and therapy of sterility and warns that it should not be considered an entirely harmless and simple procedure. The injuries may be of a chemically toxic, mechanical, embolic, and inflammatory nature.

To prevent the accidents he urges that a careful history be taken and thorough physical examination be done, and to consider and decide carefully which therapeutic procedure and contrast medium should be used. Iodism, if an iodine preparation is used, should be kept in mind, the intrauterine pressure should not exceed 150 mm. Hg and latent adnexal infections be ruled out. Because of delayed reactions the patients should be under careful observation for several weeks, and he reports two patients in whom reactions followed three and seven weeks, respectively, after the procedure. By observing careful and necessary precautions, the number and type of complications can and should be as low as with any other diagnostic procedure.

C. E. PROSHEK.

Lorset, J.: Subsequent Investigation of Patients Operated on at the Oslo Clinic From 1928-1938 for Sterility Due to Tubal Occlusion, Acta. Obst. & Gynec. Scandinav. 20: 344, 1940.

A series of 77 operations for closed tubes is reported. A follow-up revealed that nine and possibly 11 patients became pregnant following the operation. The author is uncertain about the two women who claimed to have had abortions. Among the nine definite pregnancies there were two ectopic gestations and seven full-term pregnancies.

Salpingography was performed after operation in 22 cases and the tubes were found to be patent in 17 instances. The author urges the use of salpingography following operation, and he has devised a special instrument for this purpose. He uses it during the operation and again on the fourth day, tenth day, and the twenty-eighth day after operation.

J. P. GREENHILL.

Vasciaveo, L.: Salpingotomy as Operative Treatment in Tubal Sterility, Gynecologia 18: 472, 1940.

Vasciaveo reports from the Sterility Center at the University of Turin the follow-up upon 14 patients, who had been treated by salpingotomy for relief of their tubal sterility. The majority of these operations were performed as incidental gynecologic operations rather than primarily for the re-establishment of tubal patency. The plastic tubal surgery was usually secondary to hysteropexy in the treatment of retroversion or retroflexion, else to removal of unilateral residual adnexal inflammatory disease.

Eight of the patients submitted to uterograms. Six of these cases were demonstrated to have postoperative occlusion of the tubes while two cases had bilateral tubal patency following salpingotomy. The specific techniques of the successful operations were the Martin operation in one instance and the Philipps operation in the other.

CLAIR E. FOLSOME.

Clauberg, C.: Is There a Chance for Conservative Treatment of Sterility Caused by Occlusion of the Tubes? Wien. med. Wehnschr. 91: 97, 1941.

The author answers the question in the positive. His method includes the following measures: First, a uterosalpingography with iodized oil is done. This procedure should be performed only by expert gynecologists. Second, the

patient is given a series of 12 to 25 short wave diathermy treatments to the deep pelvic tissue. The heat therapy is administered upon alternate days. Last, following the heat therapy courses, the patient is given an intramuscular injection of follicular hormone, 5 mg. every fifth day, for a total dosage of 25 to 30 mg. (250,000 to 300,000 mouse units). The author insists that the hormonal therapy must be given in the first half of the menstrual cycle.

Clauberg states that corollary to uterine growth the tubes show a correspondingly distinctive growth stimulation. He demonstrates, with roentgenographic evidence, that nonpatent tubes prior to the above-mentioned treatment, do become patent. In those patients with infantile-like uteri and demonstrable nonpatency of the tubes, he was able to relieve sterility with only the hormonal treatment. A series of halftone plates illustrate the author's evidence of convincing uterograms, taken before and after treatment.

CLAIR E. FOLSOME.

Amundsen, E.: Is Sterilization During the Puerperium Contraindicated? *Acta. Obst. & Gynec. Scandinav.* 20: 295, 1940.

When sterilization must be performed, the best time for the operation is shortly following delivery. The advantages are that the patient is still in the hospital and that from a technical point of view the operation is simple. In a series of 150 sterilizations performed shortly after delivery at the Oslo Clinic, there were no deaths. Most of the operations were performed on the third day after delivery. Local anesthesia was used in practically all the cases, and the operation employed was resection of the tubal corners. In none of the cases was there any sign of infection or embolism, although thrombosis appeared in six cases. When a series of patients operated upon before 1932 is added to the present series, it is found that the incidence of thrombosis following sterilization is about 2 per cent. The author believes that this incidence could be considerably reduced by performing the operation on the first day after delivery.

In the discussion of this paper Sund mentioned that this method of sterilization was invented by Mannen thirteen years ago. Sund has performed about 300 such sterilizations and has not observed any deaths or any serious complications.

J. P. GREENHILL.

Dippel, A. Louis: Tubal Sterilization by the Madlener Method, *Surg., Gynec. & Obst.* 71: 94, 1940.

Five clinical failures of tubal sterilization by the Madlener method were encountered in a series of 101 patients.

The areas of attempted sterilization were recovered at the time of a second sterilizing operation, from both tubes of 4 of these patients, and from 1 tube of the other. Each area was serially sectioned to ascertain the reason for failure.

One patient had a very early pregnancy at the time of the Madlener sterilization. In 2 instances considerable regeneration of the tubal lumen occurred, so that the ligating suture must have been improperly tied or placed or slipped off the knuckle. This error was bilateral in 1 case. In a fourth patient the tubal lumina were apparently completely obliterated but eventually an inferior lumen was re-established on one side by endosalpingosis. In the fifth instance, both tubal lumina were replaced by scar tissue but a small tuboperitoneal fistula apparently developed as a result of endosalpingosis on the medial side of the ligated knuckle of one tube.

The number of failures of tubal sterilization by this method should be reduced by more careful adherence to the technique as originally laid down by Madlener, although certain modifications do not seem to have increased the incidence of failures.

There were no maternal deaths associated with the 101 Madlener sterilization operations but in 369 women sterilized by other methods during the same years, 7 deaths occurred.

WILLIAM C. HENSKE.

Müller, F.: *Pregnancy After Sterilization Operation*, Zentralbl. f. Gynäk. 64: 1010, 1940.

Müller cites an interesting case in which pregnancy occurred in a young woman thirteen months after partial excision of the tubes. On opening the abdomen again, the proximal ends of both tubes were found adherent to the fundus uteri. On the left the fimbriae were found adherent between the ovarian ligament and fundus. Methylene blue solution was injected through the cervix and appeared through a fistulous opening through the uterine wall under the region of adherence of the fimbria of the left tube. The fistula was excised and sectioned and showed a lining of tubal epithelium. The author concludes that remnants of tubal epithelium left on excision of the cornual portion of the tube proliferated and canalized the fistula.

R. J. WEISSMAN.

Correspondence

Adenocarcinoma of the Vulva

To the Editor:

In the August, 1941, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY there appeared an article by McDonald, Lovelady, and Waugh entitled "Adenocarcinoma of the Vulva," in which a total of thirty-two tumors are reported. The authors state: "Thirty of the neoplasms were papillary adenocarcinomas, and because of this have been grouped together." We do not wish to take issue with the other two tumors. But the gross and microscopic descriptions and the photographs of these thirty so-called papillary adenocarcinomas are strikingly similar to the descriptions and photographs of what we called "Hidradenoma of the Vulva" in an article published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, 38: 509, 1939.

There can be no doubt that McDonald and his co-workers are describing the same neoplasms as we did. Although they mention hidradenomas of the vulva in their introductory work, they do not refer to the possible identity of hidradenoma with papillary adenocarcinoma. If they are the same type of newgrowth, as we believe them to be, it is important to determine whether they are benign or malignant so that they can be named suitably.

McDonald et al. discuss the question of malignancy:

"The problem can be brought up as to whether these papillary neoplasms represent true carcinoma or not. Because of their histologic character, it would seem better to refer to them as adenocarcinomas of a low grade of malignancy rather than simple adenomas. Metastatic growths were not found in any of the cases of papillary carcinoma. However, it would appear probable that if a sufficient number of these cases were studied, metastatic growths would be found eventually.

"From a practical standpoint it can be stated that because of the slow growth of the tumor and the slow tendency to metastasize, complete excision of the tumor together with a portion of the surrounding tissue is sufficient to effect a cure in these papillary carcinomas."

As one analyzes the various reasons given here by the writers for designating this newgrowth as malignant, one finds that the only actual evidence consists of "their histologic character." Fig. 1 of their report, they claim, shows that a "transition between the clear cells of the apocrine sweat glands and the carcinoma cells can be seen." We fail to recognize anything that we would call carcinoma. Our own cases, published and unpublished, closely resemble this histologic picture, but nowhere did we find any characteristics of malignancy.

Elsewhere, last sentence, page 305, they state that the capsule of the cyst occasionally was invaded by tumor cells. We found the same picture in our studies, but we felt that we were not dealing with invasion of the capsule but rather an artifact of sectioning. This is a common occurrence in papillary cystadenomas.

Although McDonald and his collaborators and ourselves have described the same histologic pictures, we have disagreed on the interpretation of this picture. We agree, however, on many other points: the tumors are slowly growing, they may exist for many years, metastases do not occur, mitoses are rare, the tumors are cured by simple excision, recurrences are not found. These qualities of tumors are widely accepted as the cardinal attributes of benignancy. The statement, that "if a sufficient number of these cases were studied, metastatic growths would be found eventually," sounds like rather belabored reasoning.

The classification of these obviously clinically benign tumors into Broders' Grade I and II adenocarcinoma seems to us inconsistent. The supposed usefulness of Broders' grading lies in the aid it is claimed to offer to the clinician in his therapeutic and prognostic attitude toward a given tumor. An effort to grade the degree of malignancy of apparently benign tumors is an attempt to attain the acme of confusion in terminology.

It is incumbent upon the pathologist to make the diagnosis of cancer only when he sees unmistakable evidence of malignancy. A tendency to straddle and play safe has undeniably resulted in innumerable unnecessary and risky radical operations. In the case of these tumors, there is no justification for applying the misleading term, papillary adenocarcinoma. It should be discarded. In spite of every effort we might make to convince the clinician or patient that a given adenocarcinoma is clinically benign, the appellation as carcinoma cannot fail to be disturbing. The term hidradenoma is histologically and clinically correct and preferable.

S. H. GRAY, M.D., *Director of Laboratories,
St. Louis City Hospitals*

St. Louis, Mo.
November 3, 1941.

Reply by Dr. McDonald

To the Editors:

I wish to thank you for referring Dr. S. H. Gray's comments to me in connection with an article entitled "Adenocarcinoma of the Vulva" written by Lovelady, Waugh, and myself and published in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* 42: 304, 1941.

Dr. Lovelady, Waugh, and myself feel that our position in regard to these neoplasms is stated in the paper and that very little further comment is necessary. After a thorough cytologic study, we expressed the opinion that these tumors were malignant, and we see no reason for changing our opinion at the present time. Since these tumors impressed us as being carcinomas, they were graded histologically, using Broders' criteria. Furthermore, two of our senior pathologists, Dr. A. C. Broders and Dr. H. E. Robertson, had reviewed the tumors in question and agreed with the conclusions reached.

A similar situation has prevailed in connection with the so-called carcinoid tumors of the ileum and appendix which in the past were considered by many to be benign. However, as more studies were completed, it was found that a sizable percentage of carcinoid tumors in the ileum metastasized, and present-day opinion seems to be swinging to the idea that all carcinoid tumors are slowly growing malignant neoplasms. Time alone will tell whether or not a similar situation will prevail in connection with what we have chosen to call papillary adenocarcinomas of the vulva.

JOHN R. McDONALD, M.D.

Mayo Clinic,
Rochester, Minn.
November 14, 1941.

Items

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of \$25.00 is required on registration, \$10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

The general oral and pathologic examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, prior to the opening of the annual meeting of the American Medical Association in Atlantic City, on June 8, 1942.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942. It will greatly facilitate the work of the Board if applications are filed as far as possible in advance of the closing date for their receipt.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

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(Appears in January, April, July, October)

- American Gynecological Society.** *President*, W. C. Danforth, Evanston, Ill. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Next meeting, May, 1942, Sky Top, Pa.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at White Sulphur Springs, Va., September 9-11, 1942.
- Central Association of Obstetricians and Gynecologists.** *President*, John H. Moore, Grand Forks, S. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, Des Moines, In., October, 1942.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, R. A. Bartholomew, Atlanta, Ga. *Secretary*, Robert A. Ross, Durham, N. C. Next meeting, February 6-7, 1942, Atlanta, Ga.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, W. T. Dannreuther. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.
- New York Obstetrical Society.** *President*, H. J. Stander. *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, T. L. Montgomery. *Secretary*, John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Charles E. Galloway. *Secretary*, James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, George G. Cochran. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Abraham Samuels, *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg, Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, Thomas Evans, Jr. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, John Rock. *Secretary*, Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.
- New England Obstetrical and Gynecological Society.** *President*, Frederiek L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, San Francisco, Calif., November, 1942.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

- Washington Gynecological Society.** *President*, W. J. Stanton. *Secretary*, L. L. Cokerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, E. Lee Dorsett. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, H. C. Walser. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Francis R. Irving. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, John Newdorp, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.

Books Received

THE DOCTORS MAYO. By Helen B. Clapesattle. Illustrated. The University of Minnesota Press. Minneapolis, 1941.

THE MICROBE'S CHALLENGE. By Frederick Eberson, Ph.D., M.D., Director of Laboratories, Gallinger Hospital, Washington, D. C. 354 pages. The Jaques Cattell Press, Lancaster, Pa. 1941.

ABOUT OURSELVES. By James G. Needham. 276 pages with illustrations by William D. Sargent. The Jaques Cattell Press, Lancaster, Pennsylvania, 1941.

CONTRIBUCION AL ESTUDIO DEL EMBARAZO ABDOMINAL. Por Dr. David Orta Menendez. Facultad de Medicina de la Universidad de la Habana. Tesis de Instructor, 1939.

THE TOXEMIAS OF PREGNANCY. By William J. Dieckmann, Associate Professor of Obstetrics and Gynecology, University of Chicago, etc. 521 pages, with 50 text illustrations and three color plates. The C. V. Mosby Company, St. Louis, 1941.

CLINICAL IMMUNOLOGY, BIOTHERAPY AND CHEMOTHERAPY. By John A. Kolmer, Professor of Medicine, Temple University School of Medicine, etc., and Louis Tuft, Assistant Professor of Medicine, Temple University School of Medicine, etc. 941 pages, illustrated. W. B. Saunders Company, Philadelphia, 1941.

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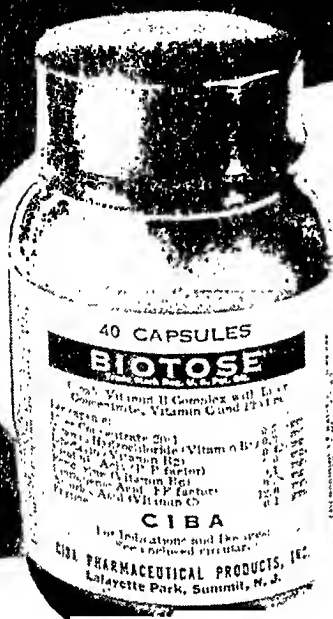
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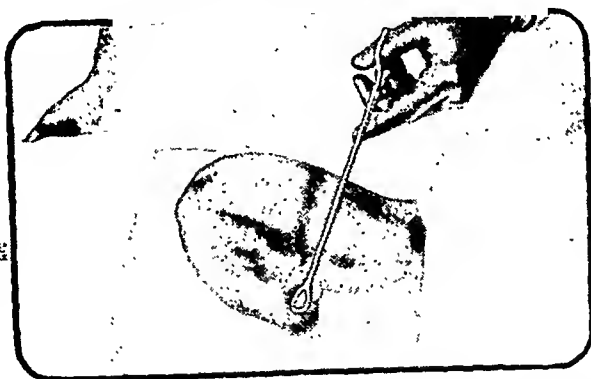
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FEBRUARY, 1942

No. 2

American Association of Obstetricians, Gynecologists and
Abdominal Surgeons

Fifty-Fourth Annual Meeting, September 11 to 13, 1941

A COMPARISON OF THYROID EXTRACT AND IODINE THERAPY IN THE PREVENTION OF TOXEMIA OF PREGNANCY*

EMMETT D. COLVIN, M.D., R. A. BARTHOLOMEW, M.D., AND
WILLIAM H. GRIMES, M.D., ATLANTA, GA.

(From the Department of Obstetrics, Emory University, School of Medicine)

DURING the past few years we have endeavored to lessen, or to prevent, if possible, the occurrence of true toxemia by the administration of thyroid extract and, more recently, by the use of iodine during pregnancy.

The rationale, supporting the use of these agents, is based on certain facts developed from previous investigations, dealing mainly with the placenta. The most important fact is that certain types of placental infarcts are so consistently associated with toxemia of pregnancy that one may predict the type of infarct which will be found in the placenta of a patient who has developed toxemia, and, vice versa, one may assert the presence or absence of toxemia during pregnancy from examination of an "unknown" formalin-fixed placenta.¹ Of great significance is the fact that the extent or mass of the infarction bears a definite relation to the severity of the toxemia.

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Another significant fact is that placental tissue contains a greater amount of arginine than any other tissue.² This amino acid, when oxidized in the course of autolysis of infarcted placental tissue, may theoretically liberate guanidine.³ Repeated injections of autolysate of placental tissue produce convulsions and death in animals.⁴ Autolysate from other tissues produces toxic effects but not convulsions.⁵

While guanidine has been demonstrated in increased amounts in pre-eclampsia and eclampsia,⁶⁻⁸ the test is not only difficult, but it is recognized that poisonous amino acids do not remain in the blood but quickly become fixed in the tissues.⁹ Repeated injections of guanidine in animals produce arteriolar spasm, hypertension, albuminuria, hypoglycemia, liver and kidney damage, increase in uric acid, convulsions, and death. These manifestations are strikingly similar to those seen in pre-eclampsia and eclampsia.

Since infarction implies obstruction in the circulation to the involved area, it is of interest to note that visible evidence of thrombosis has not only been found, affecting some of the large vessels on the fetal surface of the placenta, but a predisposing cause of thrombosis has been found in the presence of a layer or collection of fat-laden cells beneath the endothelium of many of the placental vessels.¹⁻⁴ This predisposes to roughening or breaking down of the endothelium from the trauma of fetal movements. The appearance of placental vessels affected in this manner is very similar to that seen in coronary thrombosis, and also that seen in the aorta and coronaries of cholesterol-fed rabbits.¹⁰

The physiologic hypercholesterolemia of pregnancy has long been known and recognized; also the fact that when the basal metabolism is low, the blood cholesterol is increased and vice versa. Since basal metabolism has been found to be definitely lower in the Southeast¹¹ and mortality associated with pregnancy definitely higher in this region,¹² it is possible that a greater degree of hypercholesterolemia may be a predisposing factor.

Furthermore, Hunt, Patterson and Nicodemus,¹³ acting upon this suggestion found that thyroidectomized, cholesterol-fed pregnant rabbits developed a typical eclamptic syndrome near term, whereas control pregnant rabbits, cholesterol-fed but not thyroidectomized, did not show this effect. The placentas from the rabbits having convulsions showed typical acute infarcts. The placental vessels showed piling up of fat cells beneath the endothelium to such a degree that the lumen was blocked. It appeared, therefore, that preservation of the thyroid prevented excessive cholesterol-vascular change in the placental vessels, thereby preventing infarction, convulsions, and death.

Finally, Turner¹⁴ has demonstrated that typical cholesterol vascular change is produced in the arteries of experimental animals when fed cholesterol. He further proves that the blood cholesterol content of the animals increased if cholesterol is administered in the diet. He found that the administration of thyroid extract concurrently with cholesterol prevented hypercholesterolemia and atheromatous changes

in the aortas of 89 per cent of the animals studied. Likewise, he demonstrated that potassium iodide administered along with cholesterol was effective in preventing hyperecholesterolemia and vascular changes in 91 per cent of the animals. The mechanism of this protection was obscure. In order to determine the influence of the thyroid gland, cholesterol and potassium iodide were fed concurrently to thyroidectomized animals. Thyroidectomy in itself did not cause hyperecholesterolemia or the development of atheromatous changes in the aorta. Feeding cholesterol produced hyperecholesterolemia and vascular changes regardless of the presence or absence of the thyroid gland. In thyroidectomized animals, the protective influence of potassium iodide in preventing cholesterol vascular changes in cholesterol-fed rabbits was lost.

Based on the above facts and reasoning as to the possible benefits of thyroid extract or iodine in limiting or preventing cholesterol-vascular change in the placental vessels and thus lessening the incidence of infarction and toxemia, a series of private patients was given thyroid extract (Parke, Davis & Co.) throughout pregnancy. The dose, which varied from 1.5 to 3 gr. daily was determined early in pregnancy and subsequently controlled by repeated basal metabolism tests and observation of the patient's reactions. Owing to the increased susceptibility of hypothyroid cases to toxemia, only those with minus metabolism were treated. For obvious reasons, it was not possible to make repeated blood cholesterol determinations throughout pregnancy.

At the end of the thyroid study, another series of cases was studied as to the effect of iodine treatment. The preparation originally used in dose of one capsule daily (1.08 gr.) was discontinued after a short time on account of objectionable bulk and unpleasant eructation. Lipoiodine (Ciba), one tablet daily, containing a comparable dose (1.8 gr. iodine), was substituted and found to be more palatable and free of undesirable effects. Only five cases in the iodine treated series developed visible and palpable enlargement of the thyroid, which subsided on discontinuing the drug. Iodine treatment was routinely stopped at the end of the eighth month on the presumption that inhibition of cholesterol-vascular change need not be carried beyond this stage.

Since hypertension was one of the more important criteria in determining the development of toxemia, a diastolic pressure of 80 mm. of mercury, based on the last distinct sound, was taken as the upper limit of normal. The systolic pressure being more variable and subject to more influences, was not considered sufficiently reliable. Since the diastolic pressure is 60 to 70 mm. of mercury in more than 80 per cent of normal patients throughout pregnancy,¹⁵ it is necessary to regard a rise above 80 mm. as an indication of impending toxemia, necessitating more careful and frequent observation. It is probably un-

safe to ignore a rising diastolic pressure until it has reached the generally accepted level of 90 mm. as the upper limit of normal. The associated development of retinal arteriolar spasms, increasing albuminuria, uric acid, edema, headache, and other symptoms is relied upon as further evidence.

It must not be presumed that a moderate rise in blood pressure and albumin late in pregnancy necessarily means true toxemia of pregnancy. In both the thyroid and iodine series of cases, the differentiation of hypertension due to early vascular disease and that due to true toxemia was made by retinal examination early and late in pregnancy and also by examination of the formalin-fixed placenta.

In a recent study,¹⁵ we were able to show that latent or mild vascular disease, as shown by a slight disturbance of the normal arteriovenous ratio of 2 to 3, to one between 1 to 2 and 2 to 3 or occasionally 1 to 2, and slight increase in light reflex, are present in 16 to 20 per cent of patients who show no hypertension early in pregnancy. Two-thirds of these patients develop mild to moderate hypertension and albuminuria in the last four to six weeks of pregnancy, apparently due to renal pathology and not due to true toxemia of pregnancy. The accompanying symptoms of edema and headache are very mild and there is seldom need for interrupting the pregnancy. The blood pressure is more variable and more responsive to rest in bed than in the case of true toxemia. The placentas from these cases show no toxic types of infarcts unless there has been evidence of a superimposed toxemia. The greater the disturbance in A-V ratio (1 to 3 or 1 to 4, etc.) the earlier the onset of hypertension in pregnancy. Of the patients showing disturbances in A-V ratio, nearly all were mild in type, between 1 to 2 and 2 to 3, a few 1 to 2 and rarely 1 to 3.

Since Chesley and Chesley¹⁶ have shown that the result of the cold pressor test early in pregnancy is inconstant and that the response is essentially the same in pretoxic and prenortal groups, we believe that retinal examination will prove to be more reliable.

In this study the cases were divided into early vascular disease and normal types according to the retinal findings early in pregnancy as seen in Table I.

TABLE I. INCIDENCE OF MILD VASCULAR DISEASE IN 760 CASES

GROUP	CASES	PER CENT
Mild vascular disease	171	22.5
Normal	589	77.5

Mild vascular disease group includes patients found to have increased light reflex over retinal arteries and A-V ratio between 1 to 2 and 2 to 3, occasionally 1 to 2 and rarely 1 to 3

A diagnosis of toxemia, whether superimposed on vascular disease or arising in normal cases late in pregnancy, was based on the development

of localized spasms of the retinal arterioles, increase in blood uric acid, and a greater degree of albuminuria, headache, edema, and hypertension than in vascular disease cases. Retinal arteriolar spasms are absent in hypertension due to mild vascular disease, and the symptoms and findings are milder, seldom necessitating interruption of pregnancy. Finally examination of the formalin-fixed placenta indicated true toxemia, if the toxic types of infarcts were found or vascular disease if they were absent.

Since the susceptibility to toxemia and the need for treatment were judged by the results of the basal metabolism tests early in pregnancy, the cases were divided into the following groups.

TABLE II. BASAL METABOLIC RATE IN 698 CASES

RATE	CASES	PER CENT
-10 or lower	263	37.6
-10 to 0	264	35.2
0 to +10	147	21.1
+10 or higher	42	6.1

This table does not include 62 additional cases in which basal metabolic rate was not determined

Two-thirds of the cases showed basal metabolic rates of zero or less. This finding further emphasizes that basal metabolic rates are lower in the southern than the northern states. Since a low metabolic rate predisposes to toxemia, this may have bearing on the higher incidence of toxemia in the Southeast.

Since iodine proved to be so much more potent than thyroid extract in preventing true toxemia of pregnancy, as will be shown in a subsequent table, the trend of the basal metabolic rate in the vascular disease and the normal cases, is compared in Table III, to determine whether the difference could be explained on this basis.

TABLE III. COMPARISON OF BASAL METABOLIC RATE IN 539 NORMAL CASES AND 159 MILD VASCULAR DISEASE CASES

B.M.R.	NORMAL		VASCULAR DISEASE	
	CASES	PER CENT	CASES	PER CENT
-10 or lower	208	38.6	55	34.6
-10 to 0	188	34.8	58	36.4
0 to +10	114	21.2	33	20.8
+10 or higher	29	5.4	13	8.2

The results show there is no significant difference in the basal metabolic rates in the early vascular disease and the normal groups, and the difference in the effect of iodine treatment must be explained on some other basis.

The results of the administration of thyroid extract to both normal and early vascular disease cases are shown in Table IV.

TABLE IV. EFFECT OF THYROID EXTRACT ON INCIDENCE OF TOXEMIA

GROUP	CASES	NON-TREATED	TOXEMIA	TREATED	TOXEMIA
Mild vasc. disease	83	48	7 (14.6%)	35	5 (14.3%)
Normal	240	155	34 (21.9%)	85	23 (27.0%)

Contrary to the results obtained by Hughes¹⁷ who showed a reduction of 50 per cent in the incidence of toxemia, the above analysis fails to show any benefit by treatment with thyroid extract.

The results of the administration of iodine to both normal and early vascular disease cases are shown in Table V.

TABLE V. EFFECT OF IODINE ON INCIDENCE OF TOXEMIA

GROUP	CASES	NON-TREATED	TOXEMIA	TREATED	TOXEMIA
Mild vasc. disease	88	49	3 (6.1%)	39	2 (5.1%)
Normal	349	161	41 (25.4%)	188	12 (6.4%)

For some unaccountable reason, the administration of iodine to cases of vascular disease during pregnancy fails to lower the already low incidence of toxemia in these cases, but when administered to normal cases, the frequency of toxemia is reduced almost 75 per cent. Whether this remarkable benefit is brought about through the effects anticipated in the rationale of the treatment or in some other manner, endocrine or otherwise, we are not prepared to say although the former view is favored.

Objection may be raised that the adoption of 80 as the upper limit of normal diastolic pressure permits the inclusion of too many cases of mild toxemia, which would otherwise be excluded by adoption of the usually accepted figure of 90. As we have already stated, practical experience necessitates the adoption of the lower figure inasmuch as one cannot safely ignore the early manifestations of toxemia which occur in the range of 80 to 90 diastolic pressure.

However, for the sake of comparison with the generally accepted standard of 90 as the upper limit of diastolic blood pressure in pregnancy, the cases have been divided into mild (diastolic from 80 to 90); moderately severe (90 to 100); severe (100 or above), also eclampsia and abruptio. Other symptoms and findings of toxemia were also considered in classifying the cases into these groups. Table VI shows the effect of iodine treatment in toxemias of various degrees of severity.

TABLE VI. INCIDENCE AND DEGREE OF TOXEMIA IN IODINE AND NONTREATED NORMAL CASES

GROUP	CASES	DEGREE OF TOXEMIA				
		MILD	MODERATE	SEVERE	ECLAMPSIA	ABRUPTIO
Nontreated	161	28 (17.4%)	7 (4.3%)	3 (1.3%)	1 (0.6%)	2 (1.3%)
Iodine treated	188	6 (3.2%)	3 (1.6%)	2 (1.1%)	0	1 (0.5%)

Although improvement is most marked in the mild cases, the more severe grades of toxemia are noticeably benefited. It is conceivable that prevention of cholesterol-vascular change and preservation of adequate circulation in the placental vessels lowers the incidence of mild toxemia; this in turn must be reflected in a lower incidence of the more severe forms of toxemia.

In Table VII, a comparison of the effect of thyroid extract and iodine in preventing toxemia is shown in the cases of early vascular disease.

TABLE VII. COMPARISON OF RESULTS OF THYROID EXTRACT AND IODINE THERAPY IN PREVENTING TOXEMIA IN MILD VASCULAR DISEASE CASES

GROUP	CASES	TOXEMIA	
		CASES	PER CENT
Control cases	97	10	10.3
Thyroid treated	35	5	14.3
Iodine treated	39	2	5.1

The results indicate that the incidence of toxemia superimposed on early vascular disease is reduced 50 per cent by the use of iodine, whereas thyroid extract apparently exerts no benefit.

In Table VIII a comparison of the effects of thyroid extract and iodine in preventing toxemia is shown in the normal cases.

TABLE VIII. COMPARISON OF RESULTS OF THYROID EXTRACT AND IODINE THERAPY IN PREVENTING TOXEMIA IN NORMAL CASES

GROUP	CASES	TOXEMIA	
		CASES	PER CENT
Control cases	316	75	23.1
Thyroid treated	85	23	27.0
Iodine treated	188	12	6.4

The results indicate that in normal cases as well as in early vascular disease cases, thyroid extract does not confer any protection against the development of toxemia. The administration of iodine, however, exerts a marked protection and reduces the later development of toxemia more than 75 per cent.

In Table IX, the incidence of severe toxemia, comprising the moderately severe, severe, eclamptic and abruptio cases taken as a group, is compared in the nontreated and iodine treated cases.

TABLE IX. INCIDENCE OF MODERATE AND SEVERE TOXEMIA INCLUDING ECLAMPSIA AND ABRUPTIO PLACENTAE IN 349 CASES

GROUP	CASES	TOXEMIA
Nontreated	161	13 (8.1%)
Iodine treated	188	6 (3.2%)

This table excludes mild types of toxemia.

The results indicate that the severe forms of toxemia are reduced nearly two-thirds or 60 per cent, by the administration of iodine during pregnancy.

DISCUSSION

If one attempts to evaluate the benefit of any therapeutic agent administered during pregnancy to lower the incidence of toxemia, he must recognize that certain cases developing evidences of mild or moderate toxemia late in pregnancy, are not cases of true toxemia but are cases of mild or latent vascular disease. Retinal examination early in pregnancy and again after development of toxic symptoms and findings, is of the greatest aid in differentiating vascular disease from true toxemia. Examination of the formalin-fixed placenta furnished the final proof in judging whether the toxic manifestations were due to true toxemia or to vascular disease.

It would have been desirable had the study covered a larger series of cases in both the thyroid and iodine treated groups, but the benefit of iodine in reducing the incidence of toxemia is so striking that we feel that a larger series of cases would not materially alter the results.

Furthermore, considering the fact that we have taken the last distinct sound rather than the beginning of the last phase as the diastolic pressure, also the fact that treatment has been limited to the group most susceptible to toxemia, and that a certain number of cases of toxemia occur in cases showing normal or slightly elevated basal metabolism, it is reasonable to believe that the possible beneficial results of iodine treatment have been under- rather than overstated.

We would emphasize again the usefulness of the ophthalmoscope to the obstetrician; also the satisfaction to be obtained from familiarity with the types of placental infarcts in the final classification of the case.

Inasmuch as toxemia may occur in any pregnancy, regardless of the basal metabolic rate and since lipoiodine (Ciba), in a dose of one tablet daily, is pleasant to take and is well tolerated, it would seem unnecessary to subject pregnant patients to basal metabolic tests, but routinely administer one tablet of lipoiodine daily from the end of the third month, when nausea and vomiting have usually ceased, on to full term. This dose is well tolerated, even though the patient may also be using iodized salt. The simplicity and apparent efficacy of this treatment recommends it as a valuable routine, both for private patients and for prenatal clinics supervised by departments of public health.

CONCLUSIONS

1. True toxemia and vascular disease should be differentiated in evaluating the efficacy of any prophylactic treatment of true toxemia of pregnancy.

2. The ophthalmoscope is a most valuable aid in differentiating true toxemia of pregnancy and vascular disease during pregnancy.

3. Examination of the formalin-fixed placenta for toxie types of infarcts is essential in the final classification of the disorder.

4. By the usually accepted standard, the basal metabolic rate in pregnancy is definitely lower in the Southeast than in other sections of the United States.

5. Low basal metabolism is a predisposing factor in the development of true toxemia of pregnancy and may be a contributing factor to the higher incidence of toxemia in the Southeast.

6. Hypercholesterolemia, induced both by pregnancy and a lower basal metabolic rate, predisposes to cholesterol-vascular change in the placental vessels.

7. Cholesterol-vascular change in the placental vessels is the probable antecedent to thrombosis, infarction, and true toxemia of pregnancy.

8. In pregnant animals, experimentation has shown the striking protective value of iodine and thyroid extract in the prevention of cholesterol-vascular change.

9. In women, administration of iodine markedly lowers the frequency of all degrees of toxemia during pregnancy; thyroid extract apparently confers no protection.

10. Lipiodine (Ciba) is a pleasant, well-tolerated form of iodine; it does not require an initial or subsequent determination of the basal metabolic rate and, given routinely in a dose of one tablet (1.8 gr. iodine) daily from the end of the third month to full term, gives promise of effecting a great reduction in the frequency of true toxemia of pregnancy.

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DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—The authors, among other things, stress information obtained by the arteriovenous ratio. Unfortunately their data regarding this are not yet published. The light reflex, to be of value, must be done by the

same person, at the same time of day and under constant conditions, as other disturbing factors give spasm of the retinal vessels.

For a long while the amino acids have been indicted as the cause of eclampsia, but different workers pick different acids. Johnston and Johnston think it is tyramine, others pick histamine and various other products. The authors think guanidine may be causative, but correctly state that the quantitations are a bit uncertain and that this amino acid does not remain in the blood very long.

The hypercholesterolemia of pregnancy is generally known, and there is a further slight rise in toxemia. This rise, according to our observations, is in the cholesterol esters. This unusual ratio between the free and combined cholesterol may have some significance. Our series of toxic patients show a hypoproteinemia, and it is our feeling that this lack may call for a compensatory increase in the fats and sterols in order to maintain osmotic pressure.

Iodine is one of the oldest therapeutic agents, but we have been unable to prove that it influences cholesterol metabolism in the human being.

In order to understand correctly the theme of this paper, it would seem that one should accept the placental infarct theory of eclampsia, then reason that iodine is given to alter the blood cholesterol so that there would be no vascular depositions, then no thrombosis, no infarction with its increase in arginine and thus no guanidine. The authors are careful thinkers and observers but the thesis is complicated.

DR. HERMAN W. JOHNSON, HOUSTON, TEXAS.—We like to give Dr. Young, an Honorary Member of this Society, credit for being the first one to associate placental infarction with eclampsia. I believe, however, that he had a predecessor. Young carried his theory down to a split protein which today we are not justified in doing as the chemistry of protein has made long strides since 1914.

In our earlier papers we thought like Young that the infarcted area was the source of the toxic amine. This idea was abandoned several years ago. If the toxic substance were in the infarcted area, the fetus should be more affected than the mother. Our theory now places the source of the toxic amine in the degenerated chorionic epithelium, and this being adjacent to the intervillous spaces accounts for the mother being more often affected than the child.

We believe that eclamptic toxemia is associated with the upright position, because the human female is the only animal that has eclampsia. This upright position, together with other conditions of pressure—namely first pregnancies, advanced pregnancy, oversized babies, twins, and polyhydramnios—results in stasis in the intervillous spaces. This stasis causes in various areas degeneration of the chorionic epithelium. For a number of years we assumed this degeneration of the chorionic epithelium took place but had no proof of it. It has now been shown that in the severe pre-eclamptic the syncytium is degenerated in 80 per cent of the villi and that in normal pregnancy only 20 per cent showed degeneration.

Cell autolysis then gives rise in these areas of degeneration to loosely held amino acids. Bacterial enzymes, if present in the blood, may convert the amino acids, especially tyrosine, into tyramine. If the condition of uniform pressure exists, namely living fetus and unruptured membranes, tyramine is absorbed by the maternal circulation. If absorbed, it causes in the nonsensitive patient hypertension alone. In the sensitive patient it produces hypertension plus angiospasm often leading to convulsions. Repeated skin tests show convulsive patients extremely sensitive to weak dilutions of tyramine.

DR. E. F. SHUTE, LONDON, CANADA.—I agree with Dr. Colvin on the importance of hypothyroidism in the etiology of the toxemias and on the importance of recognizing and treating toxemias *very* early, at the first albuminuria, at the first edema,

or at the first hypertension. If the treatment is not begun then one can scarcely expect to prevent their development, although their severity may be mitigated.

Patients who have a lack of thyroid do not excrete estrogen well and therefore, presumably, the estrogens pile up, producing conditions which I think are responsible for most of the late toxemias. The best antiestrogens appear to be progesterone and vitamin E. If one uses vitamin E in these late toxemias associated with high estrogen values, the dose should be large. A certain small percentage of these late toxemias are true pre-eclampsics, are associated with low estrogen values and improve on estradiol or stilbestrol. In these latter, we have used as much as 50,000 international units of estradiol two or three times a week, or 5 mg. of stilbestrol per day. Our results are of interest and will be summarized in the near future.

DR. COLVIN (closing).—In answer to a question, we encountered only 5 cases reacting unfavorably to lipoiodine. All developed tenderness and enlargement over the area of the thyroid gland which immediately disappeared when the iodine was discontinued.

In regard to the origin of placental infarcts, we remain convinced of the specificity of infarcts associated with true toxemia of pregnancy. The infarcts are on the fetal side of the circulation and due to interference of the fetal circulation in placental vessels. It does not seem logical to believe that a poisonous substance circulating in the maternal blood stream could produce localized infarcts without involving the entire exposed surface of the placenta.

In dealing with the problem of hypertension and albuminuria late in pregnancy, one must bear in mind that all such cases are not true toxemia. The ophthalmoscopic investigation of the retinal arteries early and late in pregnancy along with a carefully conducted study of the formalin-fixed placenta for acute infarcts will aid in the differential diagnosis and final classification. We have found that approximately one-fifth of our cases reveal evidence of vascular disease early in pregnancy. The increased light reflex over the sclerosed retinal arteries along with a disturbance in the arteriovenous ratio are usually the only characteristics by which such cases are to be recognized. More than 60 per cent of these patients develop hypertension and albuminuria four to six weeks before term. The management of such cases is different from that of true toxemia.

Although lipoiodine is not effective in preventing superimposed toxemia in vascular disease cases, the fact that it is capable, in doses of 4½ gr., of reducing the incidence of true toxemia approximately 75 per cent in normal cases should warrant its more extensive use.

GRANULOSA AND THECA CELL TUMORS OF THE OVARY*

WITH A REPORT OF THIRTY CASES

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THIS paper is a report of a clinical and pathologic study of 21 cases of granulosa cell tumors and 9 cases of theca cell tumors of the ovary. These tumors have all been encountered during the past twelve years.† The case histories are complete and with three exceptions include a postoperative follow-up record of from one to twelve years. The close relationship between the granulosa and theca cell type of tumor is recognized, but they will be discussed separately because of the controversy regarding the pathologic status of the latter.

The twenty-one granulosa cell neoplasms presented considerable variation in gross and microscopic appearance. The smallest tumor was microscopic in size while the largest weighed 24 pounds. The moderate-sized tumors, as a rule, revealed areas of interstitial hemorrhage, cystic degeneration, and necrosis (Fig. 1, A). The solid portions were whitish in color and of brainlike consistency. Marked friability was a constant feature of those tumors which were predominantly of the follicular type. One tumor presented gross evidence of luteinization. This tumor measured 6 cm. in diameter and the cut surface was a brilliant yellow color, presenting the appearance of a huge corpus luteum of pregnancy (Fig. 1, B). The tumors, with one exception, could be divided into the three generally accepted microscopic types: the follicular, the cylindroid or trabecular, and the sarcomatoid (Fig. 2, A, B, C). More than one type was usually present in a single tumor and frequently all three were found. One tumor was of an adenomatous type. Traut and Butterworth¹ and Varangot² have described similar tumors but they are rare (Fig. 2, D).

The diagnosis of the follicular and cylindroid type of granulosa cell tumor offered little difficulty. The pattern of growth was distinctive and the granulosa cells closely resembled the normal granulosa cell of the Graafian follicle. Tumors of the sarcomatoid type were frequently more difficult to recognize as granulosa cell neoplasms. The granulosa cells in both appearance and manner of growth had lost their distinctive

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

†The clinical and pathologic features of these cases are summarized in Tables V and VI.

tive epithelial character and resembled connective tissue cells. If sufficient sections were examined, however, areas of transition of these connective tissue-like cells to typical or nearly typical granulosa cells

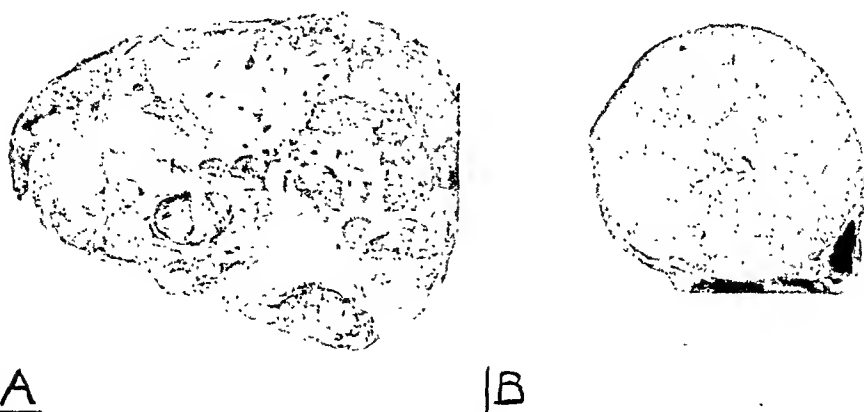


Fig. 1.—(A) Granulosa cell tumor showing interstitial hemorrhage; cystic degeneration, and necrosis. (B) Completely luteinized granulosa cell tumor. The cut surface was a brilliant yellow color. This tumor occurred before puberty.

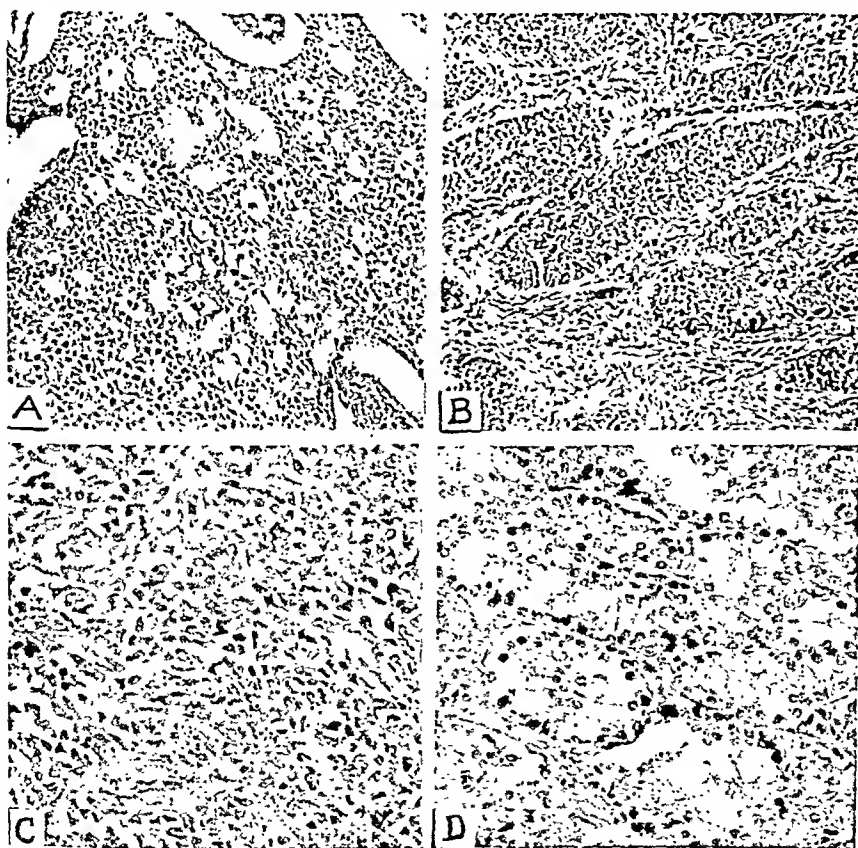


Fig. 2.—Four microscopic types of granulosa cell tumor: (A) follicular, (B) cylindroid, (C) sarcomatoid, and (D) adenomatous.

could be found, as well as a change in manner of growth from sarcoma-like to follicular or cylindroid.

As no hormone assays were made, evidence of biologic activity of the tumor was obtained from the clinical history or the microscopic examination of the endometrium. The common clinical evidence of hormone activity was uterine bleeding alternating with irregular periods of amenorrhea. Amenorrhea of three to four months' duration was common while periods as long as two years were occasionally observed. When such long periods of amenorrhea occurred during the age period of the menopause it was often difficult to determine whether the amenorrhea was due to a physiologic menopause or to the tumor. Endometrial hyperplasia of the Schroeder or "Swiss-cheese" type was the common pathologic evidence of excessive estrogen secretion. During the postmenopausal years, myometrial hypertrophy frequently accompanied the



Fig. 3.—Microscopic granulosa cell tumor. This tumor was found in an ovary removed along with a pregnant uterus at the time of therapeutic abortion.

endometrial hyperplasia while, in the one case occurring before puberty, secondary sex characteristics were precociously developed. Evidence of biologic activity of the tumor was present in 15 of the 21 cases. In 10 cases the evidence was endometrial hyperplasia and in 5 it was a clinical history of irregular uterine bleeding. In 4 of these 5 cases, the endometrium was not available for study, while in the fifth case the endometrium was in the early proliferative phase.

Of the 6 tumors which were classified as failing to produce evidence of biologic activity, 2 were associated with carcinoma of the endometrium and the uterine bleeding which occurred in these cases was attributed to this lesion. Of the remaining 4 tumors, 2 were of the follicular type and 2 of the sarcomatoid. The smallest tumor and the largest in the series were in this group of neoplasms which failed to

produce evidence of estrogen secretion. The smallest tumor was microscopic in size and was accidentally found in an ovary removed along with a pregnant uterus at the time of therapeutic abortion (Fig. 3).

In the group of 21 granulosa cell tumors, there were 5 cases of uterine fibroids as well as 2 cases of carcinoma of the endometrium. As those findings were duplicated with the theca cell neoplasms, their possible significance will be discussed later. Dockerty and MacCarty³ have reported 2 cases of carcinoma and 8 cases of fibroids in a group of 30 granulosa cell tumors.

The age incidence of the tumors (Table I) corresponds fairly closely with other reported series. Excluding the one case which occurred before puberty, 9 occurred before and 11 after the menopause. As previously mentioned, however, it is often difficult to determine whether amenorrhea occurring at the age period of the menopause is due to a physiologic climacteric or the result of the estrogen secreted by the tumor.

TABLE I. GRANULOSA CELL GROUP

Under 10 years	1 case
Over 20 years	1 case
30 years	4 cases
40 years	5 cases
50 years	6 cases
60 years	2 cases
70 years	2 cases

The postoperative follow-up record (Table II) reveals one clinically malignant tumor, a remarkably low incidence of malignancy when compared with the 15.4 per cent reported by Traut and Marchetti,⁴ 28.1 per cent, by Novak,⁵ and an estimated 25 per cent by Varangot.²

TABLE II. GRANULOSA CELL GROUP, FOLLOW-UP RECORD

NO. OF CASES	PRESENT STATE	DURATION OF FOLLOW-UP
5	Alive and well	7 to 12 years
6	Alive and well	4 to 6 years
7	Alive and well	1 to 3 years
1	Died postoperative	21 days
1	Died from recurrence	3 months
1	Unknown	

The effect of postoperative high voltage x-ray treatment was difficult to evaluate. Six patients received radiotherapy. One of these patients died three months after operation with ascites and evidence of abdominal carcinomatosis. This tumor was judged histologically malignant. Of the remaining five tumors, only two were considered histologically malignant and both patients are alive and well, one for five years and one for eight years. As no definite histologic basis for the diagnosis of malignancy has been established for these tumors, the last

two cases do not warrant any conclusions. The failure of the high voltage treatment to arrest the progress of the growth in the one case is similar to the experience of Traut⁴ who concluded that "in the malignant group of tumors x-ray is not effective in retarding or stopping the progress of the growth." Nevertheless, until more is known about the malignant potentialities of the granulosa cell tumor and the effect of irradiation on a large number of cases has been observed, it would seem wise to advise such treatment in all cases in which the tumor occurs at the time of, or after, the menopause.

Considerable variation in the rate of growth of these neoplasms was evident. One patient was observed for three and one-half years without any increase in size of the neoplasm, while the largest tumor in the series occurred in a patient, whose only complaint was a rapidly enlarging abdomen for one year. Another case demonstrated marked rapidity of growth following the intrauterine application of radium for metrorrhagia. The radium was inserted under anesthesia and no ovarian enlargement was noted at that time. Three months later a malignant sarcomatoid type of granulosa cell tumor, 16 cm. in diameter, was removed. The abdomen was filled with blood-stained fluid and the tumor showed extensive interstitial hemorrhage and necrosis. Traut⁴ mentions two tumors which were apparently unaffected by previously applied intrantrine radium.

The clinical and pathologic status of the theca cell tumor cannot be as exactly defined as that of the granulosa cell neoplasm.

Since Loeffler and Priesel¹² first described a fibroma-like tumor of the ovary, having estrogenic effects, as a fibroma theca-cellulare xanthomatoides ovarii, doubt has arisen of the actual existence of a theca cell tumor and of its biologic activity. Thomson and Sabler,⁶ in a critical review of the cases reported by Geist¹³ as well as the above authors, state that these authors "have not succeeded in proving their case as to the existence of a special group of tumors with specific naked eye and histologic appearance and typical symptomatology." Novak⁵ questions the advisability of too sharp a division between the granulosa and theca cell tumors and considers them "a species of granulosa cell neoplasm." Traut,⁴ in analyzing 54 cases of what he termed "so-called granulosa and theca cell tumors," found only 4 pure theca cell neoplasms and none gave evidence of hormone secretion.

It is not the purpose of this paper to present a critical review of this discussion but rather to outline the clinical and pathologic features of our cases judged to belong to this rather uncertain group of neoplasms.

Briefly, our diagnosis of a theca cell tumor has been made on: (1) A firm fibromalike tumor with a cut surface presenting streaks or islands of yellowish colored tissue which stand out rather prominently. In one case, the whole tumor was distinctly yellow (Fig. 4). (2) A microscopic picture of interlacing bundles of connective tissue cells with

rather broad spindle-shaped nuclei. Scattered throughout this connective tissue network are islands of epithelioid cells, either with vacuolated cytoplasm or acidophilic cytoplasm and clearly defined polyhedral cell

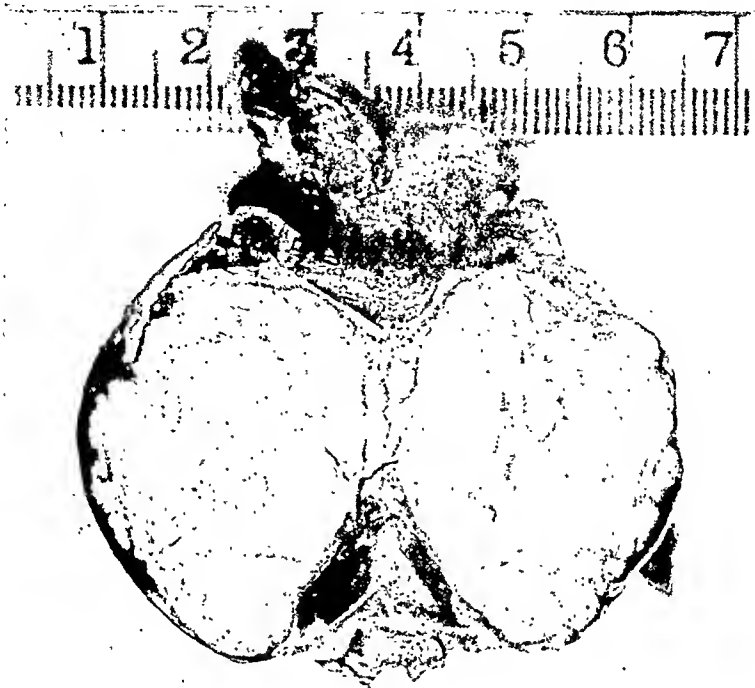


Fig. 4.—Theca cell tumor.

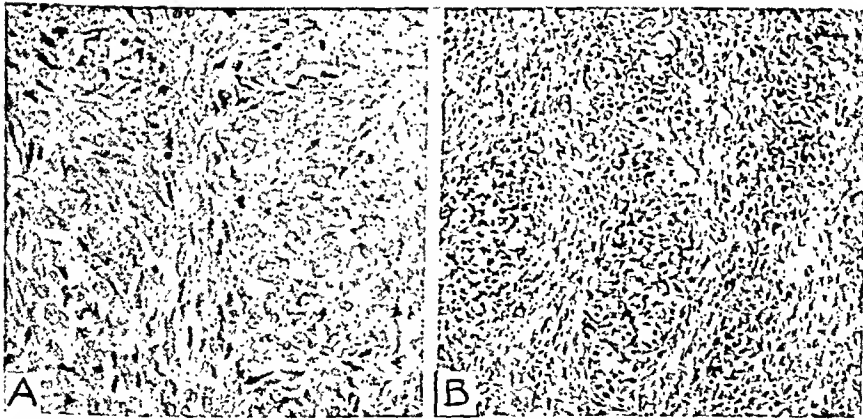


Fig. 5.—Microscopic features of theca cell tumor. (A) Interlacing bundles of connective tissue cells with rather broad spindle-shaped nuclei; (B) islands of vacuolated epithelial-like cells.

boundaries giving a luteinlike appearance to the cells. Extensive areas of hyalinization are usual. (Figs. 5 and 6, A, B, C.) (3) The presence of varying amounts of intracellular lipoid (Fig. 6, D).

Only one of the 9 tumors occurred before the menopause. In this case menstruation was normal and the endometrium was in the premenstrual phase. The remaining eight tumors were all associated with

uterine bleeding. In 5 the bleeding was associated with endometrial hyperplasia and in 3 with carcinoma of the endometrium. One of the cases of hyperplasia was atypical and four years after the original diagnosis of hyperplasia had been made a second curettage revealed adenocarcinoma. The uterus was the site of fibroids in 5 of the 9 cases. Wolfe and Neigus⁷ have recently reported one case of carcinoma of the endometrium and 4 cases of fibroids in a group of 8 theca cell tumors.

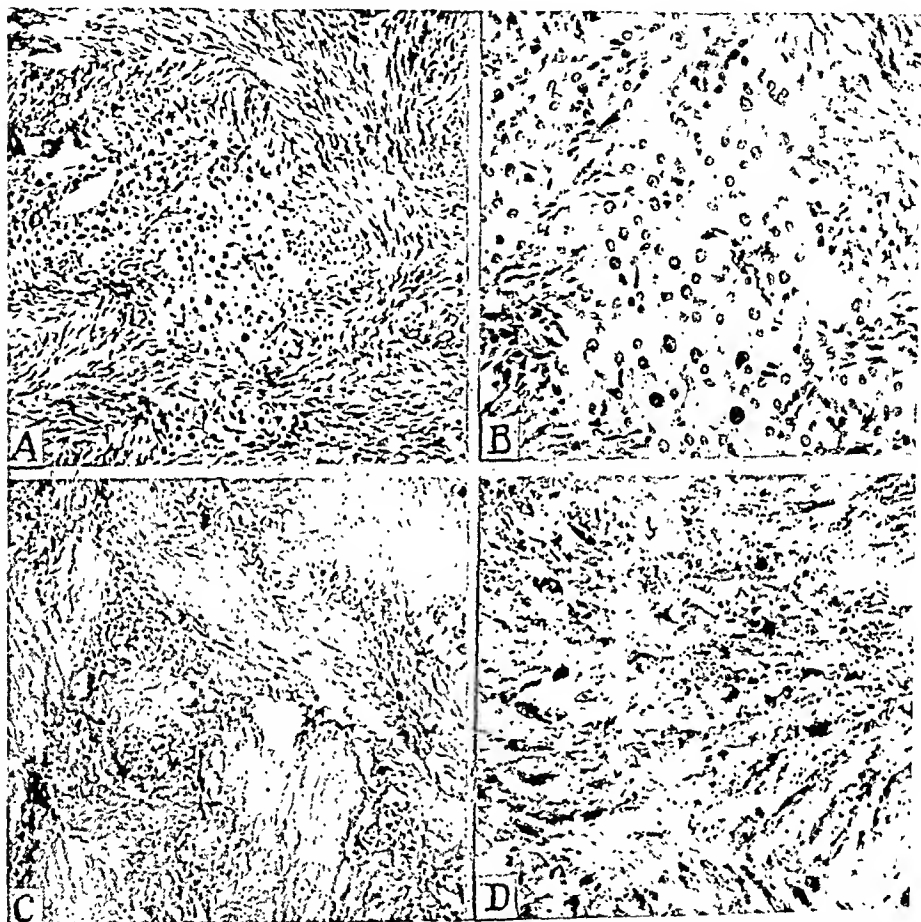


Fig. 6.—Microscopic features of theca cell tumor. (A) and (B) Low and high power of luteinized cells; (C) areas of hyaline degeneration; (D) intra- and extra-cellular lipoid as demonstrated by sudan III.

The age incidence of the theca cell tumors was later than that of the granulosa group (Table III). With one exception all occurred after fifty years of age.

TABLE III. THECA CELL TUMORS, AGE INCIDENCE

YEARS	NO. OF CASES
30-39	1 case
40-49	0 cases
50-59	4 cases
60-69	3 cases
70-79	1 case

The postoperative follow-up record (Table IV) reveals that none of these tumors has proved to be malignant. Three patients received postoperative high voltage x-ray treatment.

All the theca cell and the majority of the granulosa cell tumors were stained by Laidlaw's silver stain to demonstrate reticulum. As pointed

TABLE IV. THECA CELL TUMORS, FOLLOW-UP

NO. OF CASES	PRESENT STATE	DURATION OF FOLLOW-UP
1	Alive and well	7 years
1	Alive and well	6 years
1	Alive and well	4 years
1	Alive and well	3 years
3	Alive and well	1-2 years
1	Alive and well	6 months then lost
1	Unknown	

out by both Brosig⁸ and Traut^{4, 9} granulosa cells are reticulum free and theca cells are individually surrounded by it. In the theca cell neoplasms, chains and islands of reticulum-free cells were found in every tumor (Fig. 7, A, B). These reticulum-free cells were not necessarily those which showed vacuolization of their cytoplasm or lutein transformation. The luteinized cells when found in large clumps were almost invariably reticulum free (Fig. 8, A), whereas cells identical in appearance when few in number were occasionally individually surrounded by reticulum, but more frequently were clustered together in groups of three or four by a reticular network (Fig. 8, B). We were unable to form a definite opinion in regard to the theca or granulosa nature of these luteinized cells. In the granulosa cell tumors, particularly those of the trabecular and cylindroid type, the septa between the cords of granulosa cells contained cells enmeshed in reticulum which closely resembled theca cells (Fig. 9).

Varying degrees of luteinization occurred in both groups of tumors. In the granulosa cell group luteinization of the accompanying theca-like cells was frequently noted when such change was absent in the granulosa cells. Two granulosa cell tumors were completely luteinized (Fig. 10). The first, which occurred before puberty, was a brilliant yellow color and on microscopic examination was of the adenomatous type. Unfortunately, no endometrium was available for study in this case but the clinical history left no doubt in regard to the biologic activity of the tumor. The second granulosa cell tumor, which was completely luteinized, failed to produce evidence of biologic activity. Microscopic luteinization was not synonymous with the presence of intracellular lipid. In some of the theca cell tumors, areas showing the heaviest deposition of fat failed to present the microscopic characteristics of luteinization. It was noted also that the degree of luteinization of the tumor bore no relationship to the type of uterine bleeding or to periods of amenorrhea.

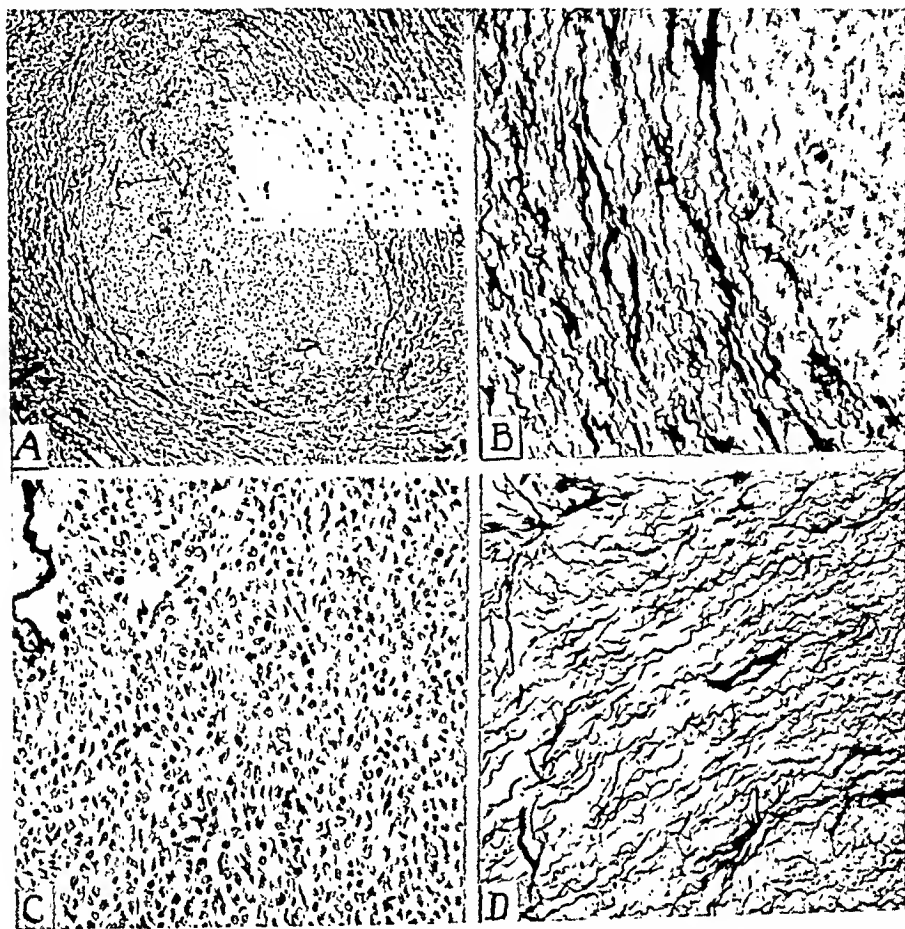


Fig. 7.—Reticulum stain. (A) An island of reticulum-free cells in a theca cell tumor; (B) high power at margin of the island; (C) sarcomatoid type of granulosa cell tumor—no reticulum; (D) reticulum of theca cell tumor.



Fig. 8.—(A) Luteinized reticulum-free cells in theca cell tumor; (B) cells similar in appearance but individually surrounded by reticulum as well as arranged in cords and small groups by a reticular network.

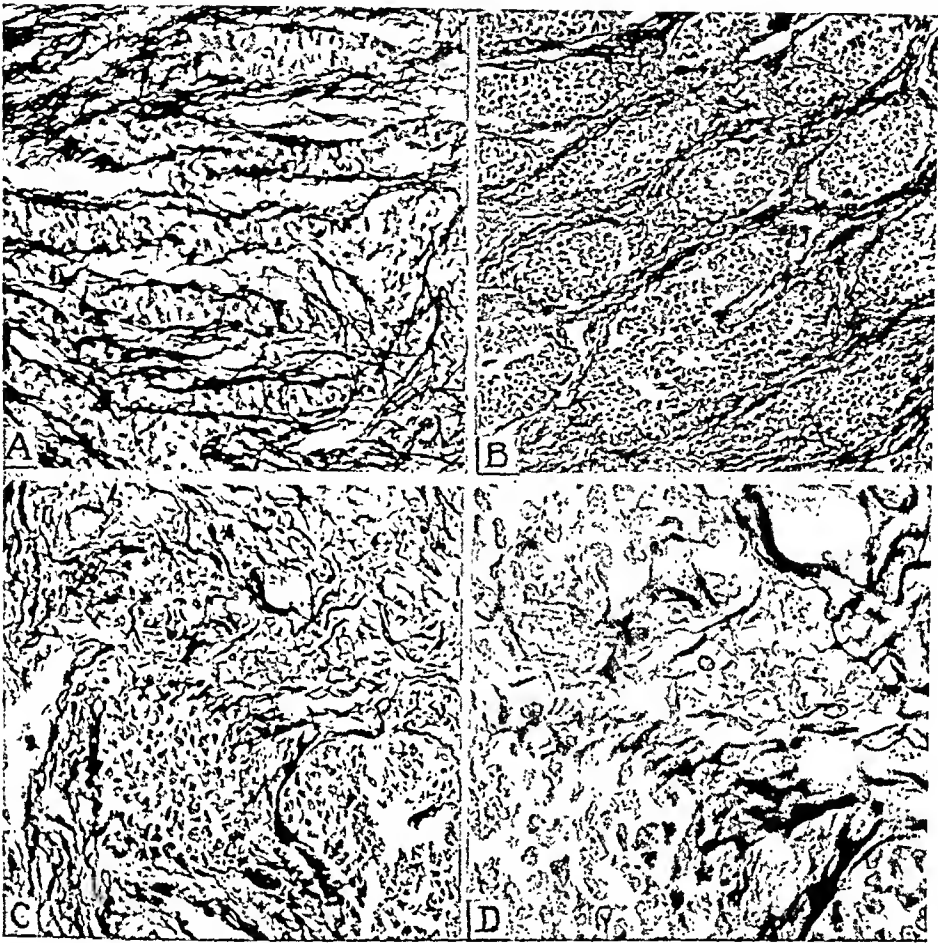


Fig. 9.—Reticulum stain, granulosa cell tumors. (A) Trabecular type; (B) cylindroid type; (C) two islands of reticulum-free granulosa cells are seen at the bottom of the microphotograph. In the septum above these granulosa cells are theca-like cells individually surrounded by reticulum; (D) high power magnification showing both types of cells.

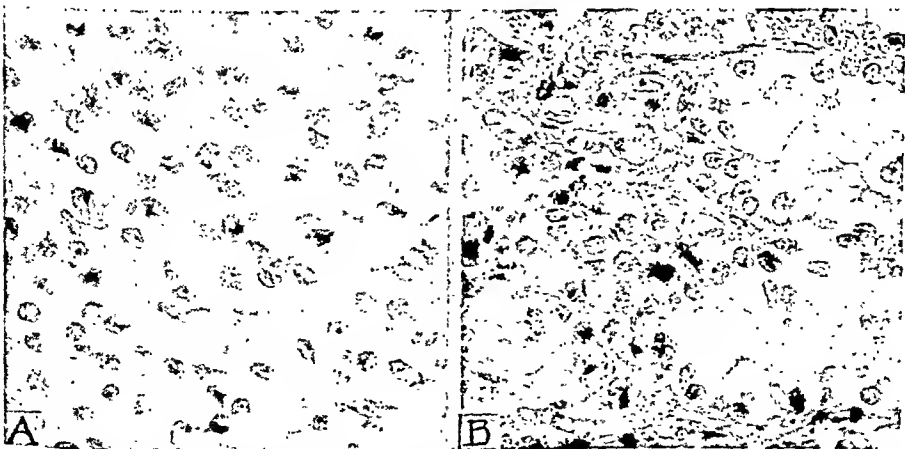


Fig. 10.—Photomicrographs of the two extensively luteinized granulosa cell tumors. (A) Luteinlike cells without vacuolization; (B) extensive vacuolization of cells in adenomatous type of tumor. Tumor B gave clinical evidence of hormone secretion while A did not.

TABLE V. GRANULOSA CELL GROUP

CLINICAL SUMMARY				PATHOLOGIC SUMMARY				
AGE	PARA	ENDOCRINE DISTURBANCE	OPERATION	FOLLOW-UP	SIZE	TYPE	ENDOMETRIUM	UTERUS
20	2	None	Oophorectomy	Alive and well 6 years	15 cm.	Luteoma	No	No
39	6	Irregular bleeding two years' duration	Hysterectomy Bil. T. & O.*	None	5 cm.	Follicular	Hyperplasia	Hypertrophied
39	3	Irregular bleeding with long periods of amenorrhea, 4 years' duration	Oophorectomy	Alive and well 7 years	20 cm.	Follicular and cylindroid	No	Hypertrophied
36	0	Irregular bleeding with amenorrhea, 3 years' duration	Hysterectomy Bil. T. & O.	Alive and well 6 years	8 cm.	Follicular	Hyperplasia	Fibroids
7	0	Vaginal bleeding and precocious development of secondary sex characteristics	Oophorectomy	Alive and well 6 years	4 cm.	Luteoma, adenomatous type	No	No
48	Unknown	Amenorrhea 2 years with hot flushes	Oophorectomy	Alive and well 2 years	24 lb.	Sarcomatoid and follicular	No	No
44	2	Irregular bleeding 2 years' duration	D & C. Bil. T. & O.	Alive and well 14 months	22 cm.	Cylindroid and follicular	Hyperplasia	No
49	4	Prolonged menstruation, flow lasting 14 days, 1 yr. duration	Hysterectomy Bil. T. & O.	Alive and well 14 months	2 cm.	Follicular and cylindroid	Postmenstrual	Fibroids
46	1	Irregular bleeding	Bil. T. & O.	Alive and well 9 years	10 cm.	Cylindroid	No	No
37	2	None, patient pregnant at operation	Hysterectomy Bil. T. & O.	Alive and well 10 months	Microscopic	Follicular	Pregnant	Pregnant

*Bil. T. & O., Bilateral salpingo-oophorectomy.

72	1	Irregular bleeding 3 months' duration	Hysterectomy Bil. T. & O.	Died postoperative	26 cm.	Sarcomatoid and cylindroid	Hyperplasia	Atrophied
57	3	Menorrhoea 3 years' duration. Vaginal bleeding 1 month	Hysterectomy Bil. T. & O.	Alive and well 1 year	20 cm.	Sarcomatoid	Hyperplasia	Hypertrophied
55	3	Irregular bleeding 2 years' duration	Hysterectomy Bil. T. & O.	Alive and well 12 years	1 cm.	Follicular and cylindroid	Hyperplasia	Hypertrophied
59	2	Endometrial hyperplasia treated by hysterectomy 1924. Ovarian tumor 1934	Oophorectomy	Alive and well 8 years	24 cm.	Sarcomatoid and cylindroid	Hyperplasia 1924	Hypertrophied 1924
60	Multiple	Irregular bleeding 2 years' duration	Bil. T. & O.	Alive and well 3 years	13 cm.	Sarcomatoid and follicular	Hyperplasia	Hypertrophied
70	1	Irregular bleeding 6 months' duration	Hysterectomy Bil. T. & O.	Alive and well 1½ years	4½ cm.	Sarcomatoid and cylindroid	Adenocarcinoma	Hypertrophied
59	0	Irregular bleeding 18 months' duration	Hysterectomy Bil. T. & O.	Alive and well 5½ years	2 cm.	Follicular	Adenocarcinoma	Hypertrophied and fibroids
66	6	Vaginal bleeding 1 week	Hysterectomy Bil. T. & O.	Alive and well 4 years	3 cm.	Follicular and cylindroid	Hyperplasia and polypus	Fibroids
51	Unknown	Vaginal bleeding 3 months' duration	Oophorectomy	Died 3 months	16 cm.	Sarcomatoid	No	No
51	2	Irregular bleeding 2 years' duration	Repair Hysterectomy Bil. T. & O.	Alive and well 7 years	3 cm.	Follicular	Hyperplasia	Fibroids
42	7	Irregular bleeding 6 months' duration	Hysterectomy Bil. T. & O.	Alive and well 6 years	2½ cm.	Sarcomatoid and follicular	Hyperplasia	Hypertrophied

TABLE VI. THECA CELL GROUP

AGE	PARA	CLINICAL SUMMARY			FOLLOW-UP	PATHOLOGIC SUMMARY		
		ENDOCRINE DISTURBANCE	OPERATION			SIZE	ENDOMETRIUM	UTERUS
37	2	Menstruation normal	Hysterectomy Bil. T. & O.	Alive and well 7 years	10 cm.	Premenstrual		Fibroids
72	0	Irrregular bleeding one year du- ration	Hysterectomy Bil. T. & O.	Alive and well 1 year	8 cm.	Adenocarcinoma		
60	1	Vaginal bleeding 4 years. Cu- retting 1934, atypical hyper- plasia Curetting 1938, carcinoma	Hysterectomy Bil. T. & O.	Alive and well 3 years	2 cm.	Adenocarcinoma		Fibroids
56	Unknown	Bleeding, 1 year duration	Hysterectomy Left oophorectomy	Alive and well 6 months (then lost)	2 cm.	Atypical hyper- plasia		Fibroids
55	5	No bleeding	Vaginal Hysterectomy Right oophorectomy	Alive and well 1 year	4½ cm.	Hyperplasia		Fibroids
63	2	Vaginal bleeding, 5 months' du- ration	Hysterectomy Bil. T. & O.	Alive and well 18 months	4 cm.	Hyperplasia		Hypertrophied
66	5	Vaginal bleeding, 9 months' du- ration	Hysterectomy Bil. T. & O.	Alive and well 6 years	8 cm.	Hyperplasia		Adenomyosis
57	2	Vaginal bleeding, 4 months' du- ration	Hysterectomy Bil. T. & O.	Alive and well 4 years	1 cm.	Adenocarcinoma		Adenocarcinoma
50	0	Vaginal bleeding, one year du- ration	Hysterectomy Bil. T. & O.	Unknown	2 cm.	Hyperplasia		Adenomyosis and fibroids

The occurrence of 5 cases of carcinoma of the endometrium in this series of 30 tumors suggests a relationship between prolonged estrogen stimulation of the endometrium, endometrial hyperplasia and carcinoma. Only one carcinoma was a localized tumor. It was of a papillary type situated in the fundus of the uterus and had deeply invaded the myometrium. The remaining 4 cases had the following common pathologic features. The endometrium was diffusely involved and the myometrium only superficially invaded. The glandular arrangement, while markedly irregular and of a bizarre pattern, was well maintained. The glandular epithelium was of a secretory type and the supporting stroma was very scant in amount. The possibility that these cases only represented extreme degrees of benign hyperplasia was considered but after careful review by the author as well as Prof. W. L. Robinson, it was decided that no diagnosis other than carcinoma was justified. However, none of these patients has died from cancer or suffered from recurrence. Is it possible that the changes in the endometrium which fulfilled the requirements for the diagnosis of carcinoma in this site were completely dependent upon the estrogen secreted by the ovarian tumor and did not represent true neoplasia?

The significance of 10 cases of uterine fibroids is equally difficult to evaluate. Excessive or prolonged secretion of estrogen has been suggested as a cause for fibroids, but there is little convincing evidence to support such a theory. On the contrary there is considerable evidence that ovarian function is normal in regard to ovulation and endometrial response in the majority of cases of uterine fibroids.^{10, 11} In 2 of these 10 cases, the endometrium was not of the hyperplasia pattern but was of the normal cyclic pattern for the known phase of the menstrual cycle. The possibility of some relationship between the estrogen-secreting ovarian neoplasm and the uterine tumors should be considered, but a definite conclusion of direct relationship is unwarranted.

SUMMARY

Thirty ovarian tumors belonging to the granulosa and theca cell group of neoplasms are reported. They correspond in age incidence, clinical manifestations, and in gross and microscopic appearance with other reported cases. They differ in one major respect, that of malignancy. Only one tumor has proved to be malignant despite a follow-up record of four years or longer in 14 cases. By means of Laidlaw's silver stain granulosa-like cells were identified in all theca cell tumors and thecalike cells in a number of granulosa cell neoplasms. While our results are similar to those reported by Traut and Marchetti, we are not yet completely satisfied in regard to the recognition of these two types of cells by this method. Tumors of the theca cell group, however, had a later age incidence and presented sufficiently well-marked pathologic differences to warrant their continued recognition as a particular

type of estrogen-secreting tumor. Two of the granulosa cell tumors were completely luteinized and one of these was of the unusual adenomatous type. The occurrence of 5 cases of carcinoma of the endometrium and 10 cases of uterine fibroids suggests a direct relationship between the ovarian neoplasm and the uterine tumors but does not warrant a definite conclusion in this regard.

Twenty-six of these tumors were encountered in the pathologic laboratory of the Toronto General Hospital, 2 in the Toronto Western Hospital, and 2 in the Ontario Provincial Health Laboratory. I am indebted to Dr. George Shanks and Dr. S. F. Penny for the surgical specimens from the 4 outside cases. I am also indebted to Drs. H. B. Coleman, J. L. Robinson, R. W. Wesley, R. R. Graham, N. Shenstone, and R. B. Hare for the clinical histories and follow-up records of their cases, as well as to my associates of the gynecologic staff of the Toronto General Hospital for similar records of their private cases. One case has been previously reported by Dr. Hare in *Canad. M. Assn. J.* 36: 620, 1937. This case which occurred before puberty was included in the present series because of the follow-up record now available and the complete luteinization of the tumor which was not emphasized in the original report.

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DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Henderson has reported findings which correspond to those of other authors, with the one exception of malignancy rate. He reports only 1 case of recurrence, while the figures of others would indicate a recurrence rate of from 28 to 35 per cent. Certainly our own experience has not been nearly as favorable as Dr. Henderson's. In our first follow-up, a fraction over 28 per cent of recurrences were noted. We now have over 100 instances of this tumor type in our laboratory, although many of these were sent in from outside sources. It is obvious, however, that granulosa cell carcinoma is a fairly common neoplasm.

All are agreed that the degree of malignancy is very much less than that of ovarian cancer in general, and statistics on recovery rates from the latter are misleading unless cognizance is taken of this fact. The striking biologic phenomena produced by some granulosa cell tumors, particularly those in prepubertal and postmenopausal patients, may lead some to forget that the majority of these tumors occur during reproductive life, when the endocrine effects produced by such tumors are inconspicuous or lacking. When such tumors occur in children, before the ovaries assume their estrogenic function, the production of estrogen by the tumor brings about the phenomena of precocious puberty. When they arise long after the menopause, the uterus undergoes hypertrophy and menstruation-like bleeding is produced, although breast changes are absent, presumably because of the unresponsiveness of the senile breast to estrogen stimulation. During reproductive

life, however, the ovaries normally produce abundant estrogen and the sex characters are fully developed, so that the production of estrogen by the tumor is a purely quantitative factor, producing sometimes menstrual excess, sometimes amenorrhea of the so-called polyhormonal type, while often menstruation is quite normal.

I have been interested in Dr. Henderson's discussion of the occasional association of uterine adenocarcinoma with granulosa cell tumors. I note that his patients who showed this association were all postmenopausal, which was of special interest to me because, as some of you know, I have urged the view that postmenopausal estrogenic stimulation of the endometrium, as seen in cases of postmenopausal hyperplasia, may be a predisposing factor to the development of adenocarcinoma.

With reference to the histogenesis of these tumors, we are coming more and more to feel that their ultimate source is the ovarian mesenchyme, which is the progenitor of both the granulosa and theca. If such a feminizing mesenchymoma develops along epithelial lines, it becomes a granulosa cell tumor or one of its luteinized derivatives. If it assumes the connective tissue form, it develops into the thecoma, which likewise may undergo luteinization. However, I have never seen a thecoma in which granulosal elements were not also demonstrable, while the same admixture is also seen in many granulosa cell growths. For this reason, the granulosa cell tumor and the thecoma should not be so sharply separated as they have been by some authors.

There is one final point which I should like to stress as regards the production of precocious puberty by granulosa cell tumors. This rather spectacular phenomenon, and the equally spectacular results accomplished by removal of the tumor, have led some to assume the presence of such a growth whenever a case of female sex precocity presents itself. Nothing could be further from the truth, for a considerably larger number of cases are due to other causes, and most often no tumor of any endocrine organ is demonstrable. In cases of granulosa tumor etiology the precocious menstruation is not associated with ovulation. In certain cases of the extraovarian group, however, both menstruation and ovulation occur. Children of this type can therefore conceive at abnormally early ages, and this is obviously the explanation of such cases as the recent one, so widely publicized, of pregnancy in a 5-year-old Chilean girl.

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—A phase of this study which is sometimes quite troublesome concerns the hyperplasias of the granulosa cells and theca cells. When correlation of these changes with the physiologic conditions is made, the question arises as to just how far the patient will carry these tissues before they reach the tumor stage.

Another interesting phase concerns the adequacy of criteria that one has before him at the time of each individual study. If a group of these cases are studied several years apart, differing criteria may be set up at each study. This is especially true with microscopic data, and differing conclusions will be reached. Diagnostic criteria are not yet very substantially established.

Another difficult factor in this study is that time is not available to study completely all of the tumor. One part of the tumor will often give an entirely different picture from that of another part. Hence it cannot be said that data are absolutely correct or comparable unless study is made of the entire tumor.

The point of theca cell tumors coming in the higher age group is interesting. Connective tissue will of course, increase as age increases, and I question whether in this particular study this does not account for the impression which sets apart the age groups. Some of the microscopic sections shown on the screen may well have been theca cell instead of granulosa cell tumors.

DR. HENDERSON (closing).—Dr. Novak talked of luteinization, which I did not have time to mention. Two of the tumors were completely luteinized, one occurring before puberty, the second later but without an associated disturbance of menstruation. In neither of these two tumors did we have endometrium available for study to say whether there was any secretory change.

I was interested in the fact that Dr. Davis felt on looking at the slides that all these tumors might well be considered as granulosa cell neoplasms. The relationship between the two types is so intimate that I would be quite willing to acquiesce in that suggestion. There were, however, differences which were more or less constant for the theca cell tumors and I grouped them together merely to draw your attention to these tumors again in order to establish their identity as a separate type of estrogen-secreting neoplasm.

MALIGNANCY OF THE OVARIES*

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IN DEALING with so complex a subject, in which there are so many unknown elements, it would seem best to divide the subject matter into its main headings, and discuss each one separately.

They naturally fall into the following subdivisions:

1. Malignancy, its meaning and properties.
2. The ovary, as the source and generator, its properties and potentialities.

MALIGNANCY

The more one studies the vagaries of tissues, and the more one becomes experienced in the interpretation of their vital phenomena, the less is one inclined to define malignancy, and still less inclined to draw a definite line between tumors with malignant properties and those with benign attributes. In the minds of most pathologists there is a no man's land between malignancy and benignity, into which we have to throw a large number of ovarian tumors of questionable parentage and still more questionable adolescence and senescence.

The ovary has types of growths which are common to other organs. But it possesses also a potentiality for types of growth that are essentially and exclusively ovarian. Does not this last statement at once rouse the thought that it is not surprising that the ovary, the mother and progenitor, possessing such tremendous potentialities for diversification of function and morphology, should also possess the faculty of having these same functions and morphology vitiated and therefore of diverting these potentialities into an equal number of abnormal growths?

In order fully to understand that statement, one must know something; yes, much, of the cell differentiation which takes place in the

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ovary, but one must understand still more the tremendous powers of vicarious function possessed by each component cell of the ovary.

Embryologically the ovarian cells are derived from the mesenchyme. At first they are undifferentiated. They all appear to be alike. This stage of development is often spoken of, but probably wrongly so, as the asexual stage. It is too deep a subject, this subject of sex, to enter into here, but *en passant*, it is not known, as yet, whether all the specific cells of the ovary are capable of forfeiting their normal quota of genes to become ova, or whether ova are set apart at an early stage of embryonic life, and the number of these once fixed cannot be increased at a later date. Oogenesis certainly goes on throughout the life of certain lower animals, but perhaps these animals are still in the embryonic state relative to man's progress in evolution. It is certain, however, that a pseudo-oogenesis goes on in some of the higher vertebrates, as I described in one of my previous works. But whether any of these pseudoformations arising out of the fusion of several cells ever reach the stage of normal oogenesis is indeed not only problematical, but very doubtful. But at least this pseudo-oogenesis shows that the body of that animal must have undergone some metabolic change reverting it somewhat to the embryonic stage when oogenesis was a normal function. The importance of this finding in the lower vertebrates is important. It may have a direct bearing upon those complex tumors, such as dermoids and teratomas, that are characteristic of ovarian tissue and are looked upon as derived from totipotent cells, such as ova, in that these tumors may contain all or some of the somatic layers of the normal embryo.

The components of the adult ovary are made up of three types of cells that are specifically ovarian. They are:

1. The specific stroma cell.
2. The membrana granulosa cell.
3. The ova.

I have put them in this order because the two latter groups are descendants of the first one. The specific stroma cell lives a labile life. It has great potentialities and a versatility in mutation that is not equalled by any other single cell of the body corporate. And what is most important is that it retains this potentiality and versatility to a great degree throughout the human sexual life, though perhaps in a progressive diminuendo as sexual life passes its maturity. As to the stroma cell's function, this does not enter into the consideration of new growths, except that it is widely maintained that vitiated function invariably precedes vitiated and ungoverned cell division.

From these stroma cells there develops a form of new growth, a description of which has not yet been published. It is a local overgrowth of these cells with a thin capsule. They are akin to fibromas, but the component cells are distinctly those of specific ovarian stroma cells, similar in morphology to stromatous endometriomas. The majority of

these tumors are microscopic and benign, but malignant types have been found, though the malignancy is of low grade and does not metastasize until the tumor has reached large proportions. They are friable and vascular and closely resemble undifferentiated granulosa tumors.

The granulosa cell, a more highly developed stroma cell, by virtue of its elevation in the cell social scale, has acquired new functions and new growth properties. Its function is that of both morphologic and topographic subservience to the dominating influence of the ovum.

Among these cells we recognize three common forms of granulosa tumors, oophoromas, folliculomas, and morphologically undifferentiated granulosa cell tumors. These three differ only in degrees of higher functional loss. The oophoromas and folliculomas are never malignant, or if they are, their morphologic functional properties are lost, though we have *no corroborative evidence that the transition ever takes place*. Granulosa cell tumors are frequently malignant, though I must confess that it is one of the most difficult, most impossible, tasks to determine by microscopic study whether any given granulosa cell tumor is malignant or not. Many of them with all the clinical hallmarks of malignancy and with extensive peritoneal contamination at operation, and with microscopic characters that denoted malignancy, have run a clinical course for years which belied our best clinical and pathologic judgment. And per contra, others seemingly benign have run a most rapidly malignant clinical course. So far there seems to be no single or complex criterion upon which a wise prognosis can be based.

The co-existence of a granulosa cell tumor of the ovary and a carcinoma of the uterus, even in young girls, offers an interesting problem of cause and effect. There are those who contend, and with a great deal of justice, that hyperestrinism is the immediate cause of ovarian and pelvic new growths. It produces in susceptible tissue an urge to grow beyond the normal relations of tissues. This contention is further supported in a theoretic way by the close chemical similarity between estrin and carcinogenic substances. The influence of estrin in malignancy seems to be borne out in the coincidence of a granulosa cell tumor and a carcinoma of the endometrium. I have two such cases, one patient at 22 years and the other at 25 years of age. They were both cases of ovarian dystrophy and had been under observation and treatment for years. There can be very little doubt that the uterine malignancy was secondary to the granulosa because this coincidence has been recorded so often in literature as to transcend the laws of chance coincidence. And there is now also very little doubt that the primary cause of the granulosa cell tumor lay in an abnormal anterior pituitary stimulation.

Luteal cell tumors, of rare origin, have more an academic interest than a clinical significance.

The ovum, with its idiosyncrasy of individual genes, is in a class by itself. It is a totipotential cell, comparable in this respect to no other cell in the human or animal body. It has only the property of division in common with other cells, but even in this respect it is individualistic. Other cells when mature reproduce only their own kind. But in the matter of differentiation the ovum is unique. When one considers that it not only can reproduce all the cell complexes of the body, but also their complex functions and transmit genealogic individual idiosyncrasies, one finds oneself in awe before a great mystery. The infinitesimally small and the infinitely great are the two extremes of which man, in his present mental development, cannot form any adequate conception. We do know, however, that the more highly an organism or machine is specialized, the more prone it is to easy upsets. It is also known from comparative physiology that quite a large percentage of ova are abnormal, either *ab initio*, or in the process of development.

From these two premises, and owing to the diversity of cell morphology usually found in dermoids and teratomas, it is generally agreed that these two forms of new growth are the expression of a vitiated metabolism upon ova. We have seen that in the lower vertebrates oogenesis may continue through the early years of sex maturity, and I have demonstrated in an old bitch that pseudo-oogenesis can and does take place. When we realize that parthenogenesis can be produced under experimental change of environment, we have in all these potent premises, factual evidence, or the conclusion that dermoids and teratomas are the result of vitiated growth in an abnormal ovum, *in situ*. Dermoids and teratomas are specifically female or male sex-organ tumors, and are found only in ovarian or testicular tissue, whether this be normally or ectopically placed. Therefore we can contend that dermoids and teratomas, being specific to ovaries, must arise out of cells that are specific to that sex organ, and consequently must arise out of ova or its progenitors. When, however, we come to the large class of pseudomucinous cysts, which are always potentially malignant, there is not such uniformity of opinion.

Many eminent pathologists claim that just as dermoids and teratoid growths are of oval origin, so pseudomucinous cysts are of the same nature and are composed almost exclusively of the endodermic layer, in the same manner as dermoids are composed almost exclusively of the ectodermic layer, and teratomas of all three component layers of the somatic body. Be that as it may, there is much to justify this opinion, and pseudomucinous cysts compose the foundation of most of the malignant papilliferous cysts of the ovary.

It is well to point out at this juncture that the popular belief is that a new growth may be benign for a long period and then, due to a change in circumstances, it may pass into a state of "malignant degeneration," meaning by this that the whole or a great part of that benign tumor may

undergo this malignant change in a large part of its substance. This is the concept that is expressed in the terms malignant degeneration of fibroids, malignant degeneration of ovarian tumors. According to the present concepts of malignancy nothing could be farther from the truth. We now believe that malignancy is usually the property of a single cell, and that all malignant cells of a tumor are derivatives of that parent cell. So if a tumor is malignant it is so from its inception, or, under the urge of growth of any tumor, a single cell of that tumor may become malignant owing to a change of circumstances in that growth. The second above-mentioned malignant change in an otherwise benign new growth is much the rarer condition, in fact, very rare condition. Something more, however, must be borne in mind. Malignant tumors have a tempo of growth, that may vary within wide limits, and in any battle between tumor and host the tempo will change according to the changes of resistance of the host. In this respect malignant new growths run a course parallel with that of infections, but in malignancy the victory is always a foregone conclusion unless some remedial measure, natural or artificial, enters to upset that certainty. The tempo of a growth, as was stated, may vary within very wide limits, and when the tempo is reduced to that approximating nonmalignant growths we may reach the no man's land between malignancy and nonmalignancy. Let us not forget in our speculation that a new growth is malignant or non-malignant from its inception, and that the variance in opinions of pathologists is merely due to our lack of knowledge of determining factors.

Malignancy may be summarized as follows:

1. The morphology of the cell composing the growth depends upon the organ from which it primarily arose.
2. The tempo of the growth depends upon the terrain and the acquired or inherited corporeal lack of resistance.
3. The rapidity of extensions and remote metastases depends upon the size of the individual new growth cells and the host's resistance.

With few exceptions ovarian malignant new growths possess a slow tempo and metastasize remotely quite rarely, and that quite late in the disease.

Another problem of new growths is to determine what causes one new growth to grow as a malignant papilloma while another grows as an infiltrating carcinoma. Some tumors combine both forms of development. It is now maintained that these two forms of extension are the same, except that the papilliferous types require a cavity (either cystic or peritoneal) for development corresponding to foliage, whereas the carcinomatous type of extension requires a supporting structure of solid tissue, corresponding to roots and earth, respectively. And just as in botany, the aerial and terrestrial are to a degree interchangeable, so it is also with malignant new growths.

The origin of the simple serous cysts of the ovary is a subject of dispute, but as these are never malignant they do not enter into this study.

The arrhenomas are in a class by themselves. Their origin is no longer a matter of dispute. In my former writings, I pointed out that woman as regards her ovaries is in a higher rank from a point of view of evolution than is man. Her ovary passed through the testicular stage of development on to the ovarian stage. The old embryologic law still holds good, that what is permanent in the lower types is transitory in the higher. In passing through the lower testicular stage to the higher, certain ovaries retain some traces of the lower male order, and under certain conditions of metabolic environment these dormant atavistic structures are lighted into activity, not only morphologic but often functional activity. Interesting as are these tumors from an evolutionary and embryologic standpoint, they are not germane to our subject as they are rarely malignant.

CLINICAL CONSIDERATIONS OF OVARIAN MALIGNANCIES

Modes of extension of malignant ovarian growths. It is generally conceded that ovarian malignancies extend almost exclusively by one of two methods.

1. By direct contamination of the peritoneal cavity by a process of implantation.
2. By lymphatic progress.

1. It is important to realize that nearly all malignant growths of the ovary begin in the medulla of the ovary. I have found malignancy of the ovary so small as to be microscopic, yet always deep in the substance of the ovarian stroma. The tunica of the ovary offers a substantial barrier to its outward progress for a considerable period of time, depending upon the tempo of the growth. Knowing this, we are always hopeful that by removing such ovaries in toto, the further extension of the disease may be circumvented. Whether the malignancy is of the papilliferous type or of the carcinomatous variety, the clinician, having no authority over the growth, hopes to intervene before the ovarian capsule has been overcome. Contamination of the peritoneal cavity takes place by one of two methods: in the malignant papilliferous cysts, the papillas gradually encroach upon the fluid content and then expand the capsule to the point of rupture. The further progress is by peritoneal implantation upon tissues that become soiled by the grafts. The opposite ovary, if not involved simultaneously in malignancy, may develop implants upon its surface, and become densely adherent in the depth of the pouch of Douglas. The ovary which is primarily affected usually has reached a considerable size before fixation takes place, and during this interval it was free to rise in the abdomen, and usually

became extrapelvic in its lie before becoming fixed by adhesions. Carcinomatous growths are usually solid and reach the peritoneal cavity by direct extension. Malignancy, however, seems often to develop in both ovaries simultaneously and independently.

2. Metastases from ovarian malignancy propagated through the blood stream are extremely rare.

Progress along the lymphatic chains and nodes, however, is extremely common, but fortunately is a late development. Ovarian malignant tumors have a relatively long period of local activity. In this respect they differ from malignancy of other organs, such as stomach, breast, etc. Even progress along the lymphatics is slow, and remote metastases are a very late development. The one notable exception to this rule is found in the rapidly growing and metastasizing granulosa-celled tumors. They fortunately are rare.

The one great hope for the surgical clinicians lies in attacking the malady in its local stage before its extensions have occurred.

To clinicians three problems at once suggest themselves.

1. Can we distinguish a malignant from a simple ovarian growth.
2. Should we endeavor to remove the primary growth when extension to neighboring structures has occurred.
3. In all cases of suspected malignancy should one remove both ovaries whether the second be visibly affected or not.

1. So far as I know there is no clinical criterion by which one can distinguish a nonmalignant from a malignant ovarian growth. Especially is this true while the malignant growth is still limited to the ovary and encapsulated. Yet this is the only period in which malignancy can be dealt with satisfactorily. Ovarian new growths are unfortunately singularly free from symptoms. Even the menstrual cycles and characters are seldom disturbed.

The advent of pain, or of free fluid in the abdomen are too often the heralds of ineradicable extensions. As previously stated ovarian malignant growths are usually slow in development. Their tempo is usually considerably less than similar growths elsewhere. This allows a long period during which the disease is purely local and offers greater chances of a hopeful complete eradication of the disease. It is unfortunate that ovarian new growth is so symptom free. So many patients consult us merely because the abdomen is enlarging. So pronounced is this freedom that many spinsters with a guilty conscience and married women come because pregnancy is suspected, owing to the abdominal enlargement. It is pathetic, however, how many cases come under observation only when the disease is too far advanced to permit any chance of total eradication.

2. When dealing with a known malignant tumor at operation, one can usually judge after a rapid survey of the abdominal cavity whether the growth is removable or not. In removing an encapsulated growth

it is often desirable to do so through as small an incision as possible by aspirating the growth and removing its contents, thereby permitting the collapsed capsule to be withdrawn through a very small opening. It is not always possible to distinguish the character of cysts by inspection, and for fear that a suspected simple cyst may eventually turn out to be multilocular, within a smooth uniformly dense capsule, exploratory perforation of the cyst by a trocar should be done very cautiously for fear of peritoneal contamination. When the mistake has been discovered, it is not always possible, in fact, rarely possible, to close the trocar puncture satisfactorily to avoid contamination during the extension of the incision and the enucleation en bloc.

When, however, upon opening the abdomen, the case presents a definite peritoneal involvement, I know of no rule which can be laid down to guide the surgeon. Only experience can be a safe judge. In these circumstances both ovaries are generally involved, one higher up, and the other bound down by peritoneal extensions in the pouch of Douglas. When, however, the ovarian growths can be removed without too much risk, even at the expense of considerable difficulty, it is thought that the period of life is lengthened. This is a debatable point, for no one can state what the tempo of that tumor was before operation, and what will be its rate of growth afterward. I have had a patient who had both ovaries removed for malignant growth, the tumors were the size of coconuts, and the retroperitoneal glands were the size of walnuts, yet she lived eight years with apparently normal health, only to die of metastasis in the end. Others seem to progress at a faster tempo after surgical intervention.

3. It is my policy to remove both ovaries whenever there is undoubted malignancy of one of them. This is not so radical a procedure as one might suspect. Most of these patients are in their late thirties or older, and spaying, as a rule, does not involve any grave consequences. In the young girl, however, the problem becomes a sentimental question. Granulosa cell tumors are notably found in the young. In two of my cases the patients were 22 and 25 years of age. I removed both ovaries, yet I know now that malignancy in granulosa tumors is difficult to define even with the microscope, though granulosa cell tumors are easily recognizable by their striking characters. Under these circumstances we would doubtless be radical in many cases and not feel any remorse.

It would seem that deep x-ray application should find in malignant ovarian disease a field of great usefulness. But, my experience is at variance with that of others, because I have found deep x-ray therapy singularly inefficient in the cure or alleviation of cases of peritoneal involvement. It is my conviction that x-rays not only do not improve, but have almost invariably broken down the patient's health and hastened death. This untoward result cannot be attributed to the roentgenologists, because these are highly trained men in various hospitals of

the city of Montreal, where instruments of high potency are at their command. So we are forced to the conclusion that the only hope for a patient suffering from incipient malignancy of the ovaries lies in early extirpation, before the disease has spread beyond the confines of the ovary. This will necessitate exploratory operation upon any suspicious tumor of the ovaries. Our attitude toward ovarian new growths must be somewhat akin to the position we adopt toward tumors of the breast. Doubtless many abdomens will be opened needlessly. So it should be our endeavor to make exploratory celiotomy free from unexpected accidents by careful preoperative study of the patients, so that eventually this operation can be recommended without fear of untoward complications. The long period of confinement of the disease of the ovary gives a wider margin of cures. But the paucity of symptoms in local new growth militates strongly against the patient, in that consultation is frequently deferred beyond the period when the disease is solely ovarian.

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DISCUSSION

DR. VIRGIL S. COUNSELLER, ROCHESTER, MINN.—In general, in all cases in which there is a tumor of one ovary, and the other ovary is normal, I advise removal of the diseased ovary. If however, there is a suggestion that both ovaries are involved I advise removal of both ovaries, the uterus, and tubes. In the presence of operable papillary ovarian cysts, panhysterectomy should be performed because implants are likely to occur in the uterus and tubes. Since the condition is often bilateral, in the case of any carcinomatous ovary either cystic or solid, I propose panhysterectomy.

I cannot agree with Dr. Goodall in his statement that these pelvic malignant growths are slow in development and metastasize late. It has been my experience and that of my colleagues that there are four different types of growth according to the grade of malignancy (Broder's classification). Those of low malignancy do grow slowly and extend late, but unfortunately many of these growths are of the high grade of malignancy, Grade 3 or 4. This is particularly true of the solid ovarian cancers. On the other hand a malignant lesion of high grade that is still intracystic is favorable for surgical cure.

At the Mayo Clinic we feel that any patient beyond the age of 37 years who has an ovarian cyst of fair size should be subjected to exploration, because the chance that these cysts are malignant increases progressively beyond this period in life. I believe that clinically it is possible to suspect malignant cysts on bimanual examination because the cyst is tense and gives the impression of being heavier than the ordinary simple cyst. It may have one or two attachments in the pelvis.

As to treatment, I am in agreement with Dr. Goodall with regard to roentgen therapy. The longer I am able to follow these cases the more I doubt the value of roentgen therapy. I believe that whenever it is possible to remove the affected organs, even though there may be some metastasis to the omentum, the patient will live just as long without roentgen therapy as with it. At the Mayo Clinic we have records of patients living twenty-five years following panhysterectomy for malignant cysts with metastasis. For some reason secondary growths in some cases regress or fail to progress following removal of the parent structure.

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Goodall's plan of subdividing granulosa cell tumors is unorthodox and seems to me unwise. For example, he applies to one group the designation of oophoroma, a term which until recently was commonly applied to a totally unrelated family of tumors, those of Brenner type. The so-called oophoroma folliculare of former years is now quite universally spoken of under the eponymic designation of Brenner tumor, and it is totally different histologically and histogenetically from the granulosa cell tumors.

I agree with Dr. Goodall as to the impossibility of prognosticating the degree of clinical malignancy of granulosa cell carcinoma on the basis of histologic criteria. The tumors which occur in prepuberal patients have seemed to be less malignant than those occurring during reproductive life, but this may be due to the fact that the striking biologic effects produced by such tumors in children, comprising the syndrome of precocious puberty, bring them to medical attention much earlier than when such tumors occur during reproductive life, when such biologic effects are not seen.

There is still some difference of opinion as to whether the cystic forms of ovarian carcinoma are always secondary to benign cystadenoma or whether they may represent carcinoma *ab initio*. There is certainly no question that cancer frequently develops in previously benign cystadenoma. Most of us have seen patients in whom large cysts have been known to be present for many years, and in whom later removal of the cysts has shown definite cancer developing in the wall of the cysts. A not uncommon observation in all laboratories is to find cancer only in a localized area of an otherwise benign cystadenoma.

From a practical standpoint, if the surgeon at operation encounters a cyst which is thin-walled throughout, it is reasonably certain to be benign, and conservative operation is indicated. If, on the other hand, a hard indurated mass is felt at some portion of the cyst, the surgeon's suspicion should be aroused, and certainly the cyst should be opened before the abdomen is closed, as this will often give additional naked eye information. If a serous cystadenoma presents only a few papillomatous outgrowths on its surface or within its cavity, it is most likely to be histologically benign, but if it is filled with a mass of necrotic papillomatous growth, it is reasonably sure to be malignant, and radical surgery is indicated. These are broad generalizations, and exceptions are of course encountered, but they demonstrate the importance to a surgeon of a knowledge of pathology. This is of much greater practical value than the collaboration of a pathologist *confre*.

With reference to the management of granulosa cell tumors, those seen in children should in general be treated conservatively, and those in reproductive or postmenopausal life radically, with individual exceptions based on such factors as age and the importance or unimportance of later pregnancies. Dr. Goodall certainly need not apologize for advocating removal of both ovaries in cases of unilateral ovarian carcinoma. Not only the ovaries but also the uterus should be removed in view of the frequency of extension to the latter organ. To do less would in the ordinary case of ovarian carcinoma be culpable, unless technical difficulties make this impossible or inadvisable.

As to postoperative radiation, its advantages are difficult to evaluate, but most of us will employ it simply to make sure that nothing of possible benefit to the patient is omitted. I do not believe, however, that it is very often of decisive value.

Finally, I should like to emphasize the inadvisability of operating on very small cysts. Many of these are of nonneoplastic, i.e., follicle or corpus luteum type, and they are of transient nature. All of you have found that at subsequent examination cysts, as large as a lemon or small orange, have completely disappeared. On the other hand, in the definitely neoplastic variety, operation is ordinarily advisable even in the absence of symptoms, not only because of the frequent occurrence of such

complications as torsion of the pedicle, but even more because of the malignant potentialities of ovarian growths, much greater, for example, than pertain to uterine myomas.

DR. JAMES K. QUIGLEY, ROCHESTER, N. Y.—I should like to report an example of the rapidity of growth of a malignant ovarian tumor. The patient, a woman of 60 years, was eurented for bleeding in December, at which time no enlargement of either adnexa was noted. A month later she had an ovarian growth the size of an English walnut, and four months later it had developed into an orange-sized tumor, at operation no metastases were discoverable, but both ovaries were removed, and radiation given. Should this postoperative radiation have been used?

DR. JOE V. MEIGS, BOSTON, MASS.—When one discovers a tumor of the ovary, if it shows papillomatous growth inside or out, one should consider doing radical surgery. All ovarian tumors can metastasize to the uterus and thence to the cervix, and I believe, therefore, that total extirpation of the uterus plus removal of both tubes and ovaries should be done. In our own series about 40 per cent of all ovarian tumors were bilateral and for that reason I think there is some predisposing anatomic or histologic abnormality. The chances are that if one ovary is involved the other probably is also.

A very small percentage of patients with solid carcinoma of the ovary live five years following operation, but 23 per cent with malignant papillary cystadenomas do live. Patients having x-ray treatment do not survive in any greater numbers than those that do not have such treatment. Nevertheless, in our series life was lengthened about three months in those who had x-ray treatment. I have some patients who are still alive who had x-ray treatment for inoperable cancer and were operated upon radically later.

One word may be said about another tumor, namely the fibroma of the ovary with fluid in the abdomen and chest. One usually assumes that such fluid is due to metastasis from cancer and that therefore no surgery should be undertaken, yet in the last year we have had 3 patients with fibroma of the ovary with pleural fluid. Patients whom we might regard as hopeless because the chest and abdomen are full of fluid should not be condemned until this syndrome has been excluded. Twenty-six such cases have now been reported; and it is certain that there are many other patients who are being overlooked.

DR. GOODALL (closing).—Of course, it is well known that fibromas of the ovary usually are associated with fluid in the chest and ascites. In patients with such accumulation of fluid in the presence of an ovarian tumor, it is often difficult to determine whether we are dealing with a simple fibroma or a malignant growth. This uncertainty is often a reason for operating.

I would not presume to answer definitely Dr. Quigley's question of whether x-ray was rightly or wrongly used in his case, but the fact that the tumor was malignant would probably have caused us to use x-ray, at least as a salve to our conscience.

With regard to the oophoromas, there was a slight misunderstanding between Dr. Novak and myself. According to my view it is a small tumor which grows slowly but which still retains some of the function of the stroma cells.

HYSTERECTOMY IN PREGNANCY, LABOR, AND THE PUERPERIUM*

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THERE is a small but definite place in the field of obstetrics, for hysterectomy. Probably no other operation so clearly demonstrates the justification for unity in obstetrics and gynecology. This paper is an attempt to correlate the indications for hysterectomy in pregnancy, labor, and the puerperium, and is based on those hysterectomies done on the obstetric service of the William H. Coleman Hospital, and the personal experience of the author. This discussion will be limited to abdominal hysterectomy, as aside from an occasional inversion of the uterus, there is little indication for vaginal hysterectomy in obstetrics.

From the opening of the Coleman Hospital in October, 1927, to Jan. 1, 1941, there have been 12,536 deliveries including all births of babies of 1,000 Gm. or more. During this period there have been 27 abdominal hysterectomies definitely associated with the parturient state.

HYSTERECTOMY DURING PREGNANCY

Tables I and II include those patients on whom hysterectomy was performed during pregnancy; Table I being those cases before viability, and Table II those past viability.

HYDATID MOLE AND CHORIONEPITHELIOMA

While chorionepithelioma may occur after abortion or labor, at least 50 per cent of chorionepitheliomas follow hydatid mole. All authorities seem agreed upon two facts, namely: (1) that hysterectomy is not a routine necessity after hydatid mole expulsion or removal; and (2) that in the presence of chorionepithelioma, panhysterectomy followed by radiation is indicated. Our great problem then is to watch patients that have had hydatid mole so that early chorionepithelioma may be discovered. I am not in agreement with those who advise the removal of hydatid mole by hysterotomy so that the interior of the uterus may be examined for evidence of invasion. In my own case, C-12875, most of the lesion was in the wall of the uterus, and an incision in the anterior wall of the uterus might easily have missed the lesion. The hydatid may be removed by sponge forceps from below and the case watched by repeated Aschheim-Zondek or Friedman tests. If the test

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TABLE I. HYSTERECTOMY ASSOCIATED WITH PREGNANCY (BEFORE VIABILITY)

	INDICATION	NUMBER	DATE	AGE	PARITY	MORBIDITY	MORTALITY	FETAL MORTALITY	REMARKS
1	Suspected chorionepithelioma (syncytial endometritis)	XC-27559	12/16/38	24	i	Yes	0	No	Syncytial endometritis
2	Chorionepithelioma	3162	5/ 1/29	28	v	Yes	0	No	No follow-up
3	Chorionepithelioma	C-12875	7/19/37	32	v	No	0	No	4-year cure
4	Interruption of pregnancy and sterilization	9600	8/20/31	34	i	No	0	Yes, 3 mo.	Tuberculosis
5	Toxemia, syphilis, and abruptio placentae	C-8841	10/ 9/35	19	i	Yes	0	Yes, 6 mo.	Hemorrhage into uterine wall
6	Interruption of pregnancy (carcinoma of cervix)	XC-47930	2/20/41	28	i Gravida iii	Yes	0	Yes, 4½ mo.	Later radiation
7	Fibroid uterus	3414	6/19/29	30	i	No	0	2 mo.	Pain in side and 3 large fibroids
8	Fibroid uterus, general debility and extreme fatigue	184	11/25/27	33	xii	No	0	Yes, 2 mo. fetus	Did laparotomy for interruption of pregnancy
9	Huge fibroids, spontaneous abortion and retained placenta	XC-42119	8/28/40	46	Gr. iii	Yes	0	Yes, 5 mo. fetus	Uterus at 5 months to xiphoid
10	Ectopic pregnancy	XC-34122	11/27/39	28	Gr. ii	Yes	0	4 mo. fetus	Ruptured into broad ligament

TABLE II. HYSTERECTOMY ASSOCIATED WITH PREGNANCY (AFTER VIABILITY)

	INDICATION	NUMBER	DATE	AGE	PARITY	MORBIDITY	MORTALITY	FETAL MORTALITY	REMARKS
11	Rupture of uterus	10159	10/23/31	20	iii	Yes	0	Yes	At 7 mo., 1 previous normal delivery, and 1 classic section
12	Rupture of uterus	C-7890	12/ 2/36	23	iii	Yes	0	Yes	7 mo. 2 previous sections (classic)
13	Large fibroid	7132	11/ 1/30	35	i	No	0	0	Baby 7-6, uterus and fibroid 6-7
14	Fibroid uterus	C-7803	7/20/35	36	i, Gr. ii	No	0	0	Degenerated necrotic fibroid
15	Post cesarean ventral hernia	XC-31473	12/20/39	26	v	No	0	0	1 previous cesarean section
16	Carcinoma of cervix	C-14246	2/ 4/38	37	ix 8 living children	No Died 1 year later	0	0	8 mo. gestation
17	Carcinoma of cervix	XC-49980		36	vi	0	0	0	7½ months gestation
18	Cervical stenosis (following cauterization)	C-4966	3/21/41	23	ii	No	0	0	Previous classic section and removal of cervical polyps by deep cauterization
19	Abruptio placentae and toxemia	XC-24504	9/17/38	24	i	0	0	Yes	Toxemia apparently improved shortly before abruptio placentae

remains positive for three months and there is in addition *definite retardation of involution* with or without bleeding, the question of hysterectomy must be given grave consideration. Under such circumstances I would advise hysterectomy, particularly if the woman had several babies, even if curettings showed no evidence of malignancy.

Sehmann recently stated as follows: "Radical surgery is indicated whenever persistent fetal elements are present, especially if irregular bleeding is a symptom, regardless of a negative Aschheim-Zondek test."

While the Friedman test is helpful, it is many times confusing because a normal pregnancy may show large quantities of gonadotropic hormone. Also chorionepithelioma may be present and the patient show only a weakly positive or even a negative test.

In our series, hysterectomy was performed three times with a tentative diagnosis of chorionepithelioma, in patients who previously had had moles. In one the pathologist's report was synektal endometritis. In another, the report was chorionepithelioma, but there was no follow-up. The third case was the author's, occurring in the presence of a weakly positive Friedman test. Complete hysterectomy, including removal of both tubes and bilateral luteal cysts, has been followed by a four-year cure. In the 15 Philadelphia cases, Sehmann reported two cases cured by panhysterectomy. It is the obstetrician's opportunity to diagnose this type of malignancy in its early stage and undue procrastination may seal the doom of his patient.

INTERRUPTION OF PREGNANCY AND STERILIZATION

In this hospital, hysterotomy and sterilization has been much more popular than hysterectomy, as 44 hysterotomies were performed for this indication. Particularly in the older group of women, I believe hysterectomy to be the preferable operation. It can be done as quickly, with less blood loss and patients have a smoother convalescence. Certainly one feels more certain of sterilization than after any type of tubal ligation or excision. It is of interest to note that the only case of abdominal wound endometrial transplant that this author has had develop, was after a hysterotomy and sterilization.

The chief objection to hysterectomy, namely, that the fundus has definite endocrine functions, has not been proved. In carcinoma of the cervix in early pregnancy, if abdominal termination is selected before radiation, supracervical hysterectomy would seem much safer than hysterotomy in the presence of the secondary infection. In this series, one case of carcinoma of the cervix was interrupted before viability by hysterectomy, as were two cases after viability. We are in agreement with Danforth who urges Porro section in those women who have carcinoma of the cervix discovered after viability. If these patients are delivered by conservative section, an occasional patient will be lost from infection.

FIBROMYOMA OF THE UTERUS

Rarely is it necessary to remove a fibroid uterus during pregnancy. However, Campbell has shown that the relation of degeneration in myomas in pregnant to nonpregnant uteri is about 9 to 1. If there is very rapid growth or degeneration characterized by pain, leucocytosis, fever, and softening of a subserous fibroid, myomeectomy is occasionally warranted. In the case of torsion of a pedunculated fibroid, this operative procedure can be safely and easily performed.

Hysterectomy was done on three cases in this series.

One patient (C-3414) had a large fibroid uterus the size of a six months' pregnancy, at two months, and complained of constant severe pain. Another (C-184) was a para xii with general debility and exhaustion, and the decision to interfere was probably influenced by this fact. The third patient is the only one upon whom I have performed hysterectomy for fibroid uterus during pregnancy, and this was after expulsion of the fetus. This patient had had two spontaneous abortions, was 46 years of age, and very anxious for a child. We attempted to carry her through, but she entered the hospital and aborted a fetus at five months. At this time the uterus was to the xiphoid. The placenta was retained. First an incision through the anterior wall of the uterus was made, the placenta separated, and delivered by an assistant from below by traction on the cord, and then a subtotal hysterectomy was done. Another patient had a hysterectomy done after section at term because of a degenerating fibroid, and another was operated upon for a large fibroid which blocked the birth canal.

Huber and Hesseltine recently have called attention to the danger of myomeectomy done at the time of cesarean section. This operation was done once at this institution and the mother died of peritonitis.

ABRUPTIO PLACENTAE

It is occasionally necessary to do hysterectomy in the very severe cases of abruptio placentae. The one patient operated upon during pregnancy was a nephritic patient who had superimposed toxemia. This toxemia had greatly improved on hospital management, and the patient was sent home. Two weeks later she entered the hospital with severe intra-uterine hemorrhage, a boardlike abdomen, and with no fetal heart tones. Hysterectomy was done as there was extensive hemorrhage into the uterine wall.

Whenever a severe abruptio placentae is admitted, transfusions are usually indicated. While operation is sometimes necessary, I have been amazed with the excellent results of conservative treatment as advocated by De Normandie, Irving, and others. With rupture of the membranes, a small dose of pituitrin and the application of a Spanish windlass, many of these patients will go into labor. Certainly this treatment is deserving of a trial before operation is resorted to. The crux of the matter seems to be whether or not the uterus can be stimulated to contract.

MISCELLANEOUS INDICATIONS DURING PREGNANCY

The patient who had hysterectomy following section at term, because of a large ventral hernia, was one who had a previous section followed by herniation of the uterus through the recti. At the time of this second operation the herniation was so great that the incision in the uterus was in the posterior wall. As the abdominal wall was of almost paper thinness, it was thought advisable to remove the uterus.

Another patient was subjected to hysterectomy at the time she was operated upon for an ectopic pregnancy of four months, that had ruptured into the broad ligament. It was felt that better peritonization could be accomplished by hysterectomy.

RUPTURE OF THE UTERUS DURING PREGNANCY

The large number of women who have had cesarean section are subject to this real danger throughout a following pregnancy. In this series there were three patients all at about seven months' gestation, who entered the hospital with rupture of the uterus. All had previous classic cesarean sections. Two had not been in labor and one had had four hours of labor. Fortunately all had an early diagnosis, a hysterectomy, and all recovered. In another case there was a small opening in the old incision so the scar was freshened and the uterus left undisturbed.

He who is faced with the decision for an initial cesarean section must take into consideration the possibility of rupture in a following pregnancy. If there was no other advantage of the low cervical over the classic operation than the increased protection against rupture of the uterus in a following pregnancy, I would select the former.

HYSTERECTOMY DURING LABOR

In addition to the patient previously mentioned who had a rupture of the uterus develop after four hours of labor, there were two traumatic ruptures occurring during labor.

The first had had attempted forceps in the home and then three ampoules of pituitrin. The second patient was a para xii with a transverse position. Our resident felt the uterus rupture while attempting to loosen the shoulder girdle. Immediate hysterectomy and transfusions were life saving in these cases.

The one case of fibroid blocking the birth canal was operated upon before labor but in case of doubt there is every reason to give such a patient a trial labor. No case of abruptio placentae or placenta previa in labor was subjected to hysterectomy.

A para vii was subjected to cesarean section plus hysterectomy after she had been in hard active labor many hours with failure of a scarred cervix to dilate.

TABLE III. HYSTERECTOMY ASSOCIATED WITH LABOR

	INDICATION	NUMBER	DATE	AGE	PARTY	MORBIDITY	MORTALITY	FETAL MORTALITY	REMARKS
20	Rupture of uterus	5471	4/ 6/30	27	iii	No	0	Yes	4 hours' labor. Previous classic section
21	Traumatic rupture of uterus	C-6033	8/10/34	27	iv	Yes	0	Yes	3 previous normal deliveries. 12 vaginal examinations in home. Forceps attempt for two hours. 3 ampoules pituitrin
22	Traumatic rupture of uterus	C-12232	2/ 6/37	42	xi	Yes	0	Yes	Transverse position. Uterus ruptured while attempt at version was being made
23	Cervical dystocia	C-14060	10/16/37	43	vii	0	No	No	Long labor

TABLE IV. HYSTERECTOMY ASSOCIATED WITH THE PUERPERIUM

	INDICATION	NUMBER	DATE	AGE	PARTY	MORBIDITY	MORTALITY	FETAL MORTALITY	REMARKS
24	Necrosis of fibroid	XC-35438	5/22/40	32	ii	Yes	0	0	6 weeks after precipitate delivery
25	Infected fibroid	2993	5/ 1/29	36	ix	Yes	0	0	Transverse position delivered by version
26	For sterilization; vascular renal disease and recurrent toxemia	XCL-25740	7/19/40	24	Gr. ii	0	0	Yes	Delivered macerated fetuses on Oct. 10, 1938, and June 29, 1940
27	For sterilization nephritis and recurrent toxemia	C-4188	8/17/36	32	P.v	Yes	0	No	Toxemia in 3 pregnancies. Eclampsia in one

CESAREAN SECTION IN THE INFECTED PATIENT

We have all seen cases which have been mishandled in labor with otherwise absolute indications for cesarean section. Not always is the baby dying, and it is only human that we should shrink from craniotomy. The recent publication of a new and ingenious technique of extraperitoneal cesarean section by Waters has added much interest to this problem. If the spill is the major thing in the production of peritonitis in cesarean section, then our problem is solved by extraperitoneal operation. Waters states as follows: "Cesarean hysterectomy can not conceivably be better than a true extra peritoneal operation except in the 15 to 20 per cent group of fatal sepsis through uterine wall and lymphatics, and even in this group one may question its effectiveness." My own conception of this problem has been stated in a previous paper. I am convinced that the spill is not the greatest factor in the production of peritonitis. In two women dying from postcesarean peritonitis at this Institution, autopsy showed infection and necrosis in the uterine incision. The peritoneum will usually stand one severe insult but with repeated insults from an infected uterine incision in the peritoneal cavity, peritonitis is likely to occur. In other words, a uterine incision in the peritoneal cavity is most dangerous in these cases. The low segment incision completely covered with visceral peritoneum is safer. In comparing this operation with the extraperitoneal, it would seem only just to include drainage of the retrovesical space as Waters does in his operation. Safest of all, though sacrificing the uterus, would seem to be cesarean section plus hysterectomy, as only the cervical stump incision is left to suppurate, the large infected organ is removed, and the uterine vessels ligated. The publication of more necropsy material in failures of the various types of operation, will do much to clarify this problem.

HYSTERECTOMY ASSOCIATED WITH THE PUERPERIUM

An infected degenerated fibroid may be an indication for hysterectomy during the puerperium. One patient in this series was delivered by version and extraction because of transverse position. She had a large fibroid, and the puerperium was characterized by fever and subinvolution. Hysterectomy was done nineteen days after delivery. A second patient was operated upon six weeks after delivery. The author has had one case where a submucous fibroid was delivered through the cervix after the patient had returned home from the hospital. This was removed from below by means of the cautery. Two patients were operated upon for purpose of sterilization on the fifteenth day of the puerperium because of malignant hypertension and recurrent toxemia.

Autopsy on one patient, dying shortly after delivery from hemorrhage, revealed an undiagnosed submucous fibroid and a partial placenta accreta. One other patient with partial placenta accreta was treated by manual removal.

In connection with the puerperium, an unusual ease of placenta spuria accreta, or partial accreta, is worthy of comment. The author did a transverse cervical cesarean on this patient (G-12097) at St. Vincent's Hospital, Nov. 15, 1937, because of a large baby with frank breech presentation and a small justo minor pelvis. The placenta presented through the incision and was delivered by slight traction. It seemed to be complete and was also reported so by the pathologic laboratory. On the twelfth postoperative day, preceded by nine days of normal temperature, the patient had rather profuse hemorrhage and pulse was elevated to 100. She was transfused and went home on the twenty-second day apparently in excellent condition with a red count of 3.4 million and a hemoglobin of 70 per cent. Four days later, at home, she suddenly had another profuse hemorrhage and was returned to the hospital. Upon admission she was still bleeding and was very anemic. She was taken to surgery where the cervix was found dilated to about 3 or 4 cm. Blood clots were removed from the uterus and tissue attached to the anterior wall could be felt with a sponge forceps. The tissue could not be removed but two or three small pieces were pulled away and found to be placental tissue when examined at the laboratory. The uterus was tightly packed. The next day the patient had a chill and temperature rise to 104° F. With a diagnosis of placenta accreta, a subtotal hysterectomy was done and the packing not disturbed until the uterine arteries were clamped, after which it was removed from below. The patient was transfused twice and recovered after some five days of temperature elevation.

The gross pathology showed a uterus of 100 mm. in diameter. There was adherent placental tissue in the upper right hand corner of the cavity of the fundus, 50 mm. long, 50 mm. wide, and 20 mm. thick. Chorionic villi seemed to dip down into the uterine muscle with absence or marked degeneration of decidua basalis. The tissue and gross specimen was submitted to a second pathologist, who concurred in the diagnosis.

THE VALUE OF INTRAUTERINE EXAMINATION AT THE TIME OF CESAREAN SECTION

Because of the experience of the above case, I determined to make it a point to explore thoroughly the uterus at the time of cesarean section. Little is stated in textbooks on obstetrics, about the conduct of the placental stage at the time of cesarean section, except that the uterus should be wiped free from membranes. In the classic section, the fundus is usually open for a clear view but in a low cervical operation the fundus is a cavity opened at the lower end, usually inaccessible to visualization. Yet there is always the possibility of abnormal placental attachment, the presence of a submucous fibroid or of injury to the uterus. Further justification of this procedure was emphasized to me by the following case.

Case Report.—E. M., a primipara, with an android type pelvis of the dystocia dystrophia syndrome type, had sharp pains in the epigastrium which doubled her over, after lifting a heavy piece of coal to the furnace.

She had continuous pain the remainder of the day. Her pulse and fetal heart tones were within normal limits. Pain continued and she entered the Methodist Hospital early the next morning in active labor. At 3 P.M. the patient had complete dilatation but station was -2, and there was marked overriding of the head with membranes having been ruptured for about six hours.

I did a transverse cervical cesarean; the baby was delivered and cried immediately. However, a swelling of one hip was present. The placenta was removed and exploration of the fundus revealed a large rupture of the roof of the uterus through which the hip had formed a perfect tampon. Some old blood was found in the upper abdomen. Immediate hysterectomy was followed by an uneventful recovery, the patient having no morbidity in the puerperium.

The rupture could easily have missed detection and the lower segment section completed. Hysterectomy was in my opinion definitely indicated.

Routine packing of the uterus, with the lower end of the pack attached to a shuttle of the DeLee type and placed through the cervix, will obviously reveal any marked stenosis of the cervix. Coleman's case (C-4966) was a patient who had had a previous section and some months before the present pregnancy she had had a very deep cauterization for cervical polyps and endocervicitis. At the time of this section I was unable to find an opening in the cervix and after the transverse cervical section, did a hysterectomy which was followed by the usual smooth convalescence. Phaneuf is the only operator I have witnessed who puts on a second glove and examines the cervix at the time of section. If one does not pack the uterus, routinely, this is an excellent procedure.

SUMMARY AND CONCLUSIONS

A review has been made of the 27 hysterectomies associated with pregnancy, labor, and the puerperium at the Coleman Hospital during the time interval embracing 12,536 deliveries. This operation may be the most conservative obstetric operation in certain situations. In this series there was no maternal mortality. Early diagnosis, hysterectomy and radiation is our hope of lowering mortality from chorionepithelioma. In many cases, hysterectomy is preferable to hysterotomy for interruption of pregnancy and sterilization. In degenerated fibroids and fibroids blocking the birth canal, cesarean section at term followed by hysterectomy is the safest procedure, myomectomy being reserved for pedunculated, or easily accessible subserous fibroids. In complete rupture of the uterus early hysterectomy and transfusions are life saving. Severe abruptio placentae occasionally demands section plus hysterectomy but not until conservative management has failed. Placenta accreta when present to any extent, is an indication for hysterectomy. The author considers cesarean section plus hysterectomy the safest abdominal procedure in the infected candidate for cesarean. Thorough intrauterine examination is advocated at the time of cesarean section for evidence of submucous fibroid, abnormal placental implantation or unsuspected injury to the uterus.

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DISCUSSION

DR. LOUIS E. PHANEUF, BOSTON, MASS.—In recent years there has been a tendency to decrease the number of hysterectomies following cesarean section, because of the improvement of the technique of the extraperitoneal operation. From the standpoint of infection, many obstetricians feel that they will accomplish as much with the Waters' type of extraperitoneal cesarean section as they would with hysterectomy.

There are cases, however, as shown by Dr. Gustafson, where the existence of a fibroid or of a placenta accreta make hysterectomy necessary. Dr. Gustafson's results following the removal of the uterus after cesarean section have been very satisfactory as shown from his figures. Personally, I have done between 30 and 40 Porro cesarean sections with gratifying results. The convalescence usually is simpler than when the uterus is retained because the process of involution is eliminated.

While I agree that extraperitoneal cesarean section will be responsible for the decrease of radical operations in the presence of sepsis, I feel that the indications brought out by Dr. Gustafson will stand, and that there will always be a place for cesarean-hysterectomy in the practice of obstetrics.

A STUDY OF 104 CASES OF UTERINE FIBROIDS ASSOCIATED WITH ARTERIAL HYPERTENSION*

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BE NOT the first by whom the new are tried, nor yet the last to lay the old aside." Can our predecessors admonish us, for today medical literature is filled with the new, but have we learned all we can about the old?

Previously, arterial hypertension has been shown to occur in at least forty-seven syndromes, and grouped under the headings of (1) neurogenic, (2) endocrine, (3) cardiovascular, (4) renal, and in a larger heterogeneous group (5) essential or malignant hypertension.

The works of Goldblatt,⁵ Harrison,⁶ Blalock,⁷ and Page⁴ on experimental renal hypertension and the isolation of renin, renin activator and angiotonin and their effects upon hypertension suffice as an example of the new work on hypertension. Discussions of uterine fibroids and

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arterial hypertension have been periodic in the medical literature since 1885, and yet the questions are far from settled. The association presents a far more complex problem than hypertension alone.

I wish to present a study of 104 cases of uterine fibroids with arterial hypertension in the hope that further study of this subject may be stimulated.

A criterion for the selection for this series began two years after a hysterectomy for uterine fibroids. All cases reviewed had an admission blood pressure of 165/85 or higher. This series was closely followed in an endeavor to ascertain whether the risk taken in these severely handicapped cases was justified and their salvage was satisfactory.

It has been stated no man should judge the results of his surgical handiwork in the female pelvis unless two summers have passed.

The majority of these patients were on relief or completely incapacitated because of discomfort produced by the fibroids, or the combination of fibroids with myocardial failure. Under the conditions of pain or incapacity one might hesitate to institute surgery when there is little to offer other than relief of pain, and the advisability of taking a great risk may be questioned unless one has a reasonable assurance of the results.

For a period of six years, from 1933 to 1939, there were 708 cases of fibroids admitted to the Louisville City Hospital; 104 of these women were hypertensive; about every seventh patient with fibroids in this series had hypertension. It might be of interest to note that there were 98 colored patients and only 6 white patients, showing the greater predominance of fibroids, a ratio of 16:1, in the colored race. The ratio is usually 9:1. Our youngest patient was 24 years, the oldest 69, both colored (Table I). The average age for both groups was practically the same, 41 years.

TABLE I. AGE AND MARITAL STATUS

RACE	AGE	WEIGHT	MARRIED	DIVORCED	CHILDREN	MISCARRIAGES
White 6	Youngest 36 Average 41 Oldest 54	Lowest 130 pounds Average 157 pounds Highest 185 pounds	2	4	4	Total 3
Colored 98	Youngest 24 Average 40.8 Oldest 69 51 under 40 47 over 40	Lowest 105 pounds Average 156 pounds Highest 235 pounds	8 single 44	46	100 living 36 dead 26% stillbirths	Total 42

A tendency throughout was to obesity, with an average weight of 157 pounds. It has been shown that there is a definite rise in blood pressure increasing with weight for all age groups, and it is three times more frequent in the obese group; these women are nine times as likely to develop arterial hypertension as those of normal weight. We are thus confronted

with the question, is it the tendency to obesity in such a group which produces the hypertension or the glandular imbalance which has a tendency to develop obesity? The triad of obesity, glandular disturbance and hypertension are frequent findings. Are they causative factors or results?

Fifty-five of the group were 40 years or younger, while 49 of them were over 40 years, the oldest being 69. All but 8 colored women had been married but all had been pregnant, a total of 100 living children, 36 dead; 26 per cent of the deaths were stillbirths. In this group there were 45 miscarriages, making a total of 1.6 pregnancies to each case. This is in contradiction to the statement that women with fibroids are infertile, or women who do not become pregnant develop fibroids. General statements are usually incorrect. Women with fibroids may have proportionately as many children as other women but they have had their children earlier in life.

A study of the clinical symptoms (Table II) revealed the predominant cause of incapacitation to be pain, especially lower abdominal pain or pelvic weight, which was exaggerated when the patient was on her feet. This occurred in 60.1 per cent of the patients as the chief complaint.

TABLE II. CLINICAL SYMPTOMS

RACE	CHIEF COMPLAINT	SYMPTOMS	FINDINGS
White 6	Pain 4—66.6%	Discharge 3—50.0%	Cardiovascular disease 4— 66.6%
	Bleeding 3—50.0%	Weakness 2—33.3%	Fibroids 6—100.0%
	Enlarged abdomen 3—50.0%	Dyspnea 2—33.3%	Pelvic inflammatory disease 2— 33.3%
	Tender abdomen 3—50.0%	Ankle edema 1—16.6%	Cervicitis 4— 66.6%
	Headaches 3—50.0%	Constipation 4—66.6%	R. V. O. 1— 16.6%
			Ovarian cyst 1— 16.6%
Colored 98	Pain 60—60.1%	Discharge 48—48.9%	Cardiovascular disease 46— 46.8%
	Bleeding 34—34.6%	Weakness 18—18.2%	Fibroids 98—100.0%
	Enlarged abdomen 24—24.4%	Dyspnea 26—26.4%	Pelvic inflammatory disease 30— 30.6%
	Tender abdomen 9— 9.1%	Ankle edema 20—20.4%	Cervicitis 24— 24.4%
	Frequency 27—27.5%	Constipation 46—46.8%	R. V. O. 18— 18.2%
		Headaches 29—29.6%	Ovarian cyst 3— 3.0%

Vaginal bleeding associated with anemia was the next most distressing symptom and occurred in 34 per cent of the cases. Enlargement and tenderness of the abdomen ranked third in prevalence of symptoms. It is to be noted that the subjective symptoms were more marked in the white than the colored race.

Other symptoms were complaints of weakness, shortness of breath, edema of ankles, etc., associated more with the anemia or cardiac disturbances than with the mechanics of pelvic pathology.

On initial examination 50 patients, or 48 per cent, had a diagnosis of cardiovascular disease, and in some cases there had been eight years of previous medical treatment for a heart condition.

Pelvic inflammatory disease was present in 30 cases of the colored patients. There were relaxed vaginal outlets in 18 of these. This finding is often overlooked in examination, but is of great importance because, while the fibroid may fill the pelvis, it acts as a support. If one removes a fibroid in the presence of relaxed vaginal floor, usually within one year the symptoms of pelvic discomfort are greater than with the previous condition; therefore it is of the greatest importance in these cases to insure a satisfactory pelvic floor after the fibroid has been removed. Our findings are that, in general, 27 per cent of the patients with fibroids have relaxed vaginal outlets which necessitate perineal repair.

Our laboratory findings (Table III) reveal the greatest anemia in the colored cases. It seems incredible that persons could exist with hemoglobin ranging from 24 to 32 per cent as were recorded upon admission; however, the average was 71 per cent by the Sahli method. In some of the inflammatory cases there was a leucocytosis.

TABLE III. LABORATORY FINDINGS

RACE	R.B.C.	W.B.C.	HG. (SAHLI)	WASSER- MANN	URINE	N.P.N.	UREA CLEAR- ANCE
White 6	Lowest 3,582,000 Average 4,073,000 Highest 4,840,000	Lowest 3,400 Average 6,700 Highest 10,000	Lowest 60% Average 70.4% Highest 85%	Positive 1 16.6%	Albumin 2	Lowest 24.0 Average 25.1 Highest 26.0	Normal 80-120 Average 100%
Colored 98	Lowest 1,680,000 Average 3,910,000 Highest 5,270,000	Lowest 2,600 Average 8,180 Highest 32,350	Lowest 30% Average 71.6% Highest 90%	Positive 26 37.7%	Albumin Trace 45	Lowest 24.0 Average 30.1 Highest 39.6	Lowest 45% Average 77% Highest 117%

Evidence of syphilitic infections was present in 16.6 per cent of the white women and in 37.7 per cent of the colored cases. This is slightly higher than the general average of positive serologic reports, which in the Louisville City Hospital was about 3 per cent for white and 23 per cent for colored individuals. This higher incidence of syphilitic infections may have a bearing on the increase of hypertension; we know that vascular changes are frequently the result of syphilitic infections.

About 50 per cent of the patients had a trace of albumin in the urine, and practically no cellular pathology of significance. As far as routine urinary tests are concerned as a single test, or even in a series they are of little value in determining kidney capacity or damage. We find that a carefully carried out Mosenthal test is of some benefit in determining renal damage.

Page⁸ has demonstrated the use of newer renal function tests with diodrast and phenol red, which are used to measure the renal blood flow, and inulin, in measuring the efficiency of tubular tissue. In hypertension he found the renal blood flow is decreased while the glomerular filtration and tubular mass are increased.

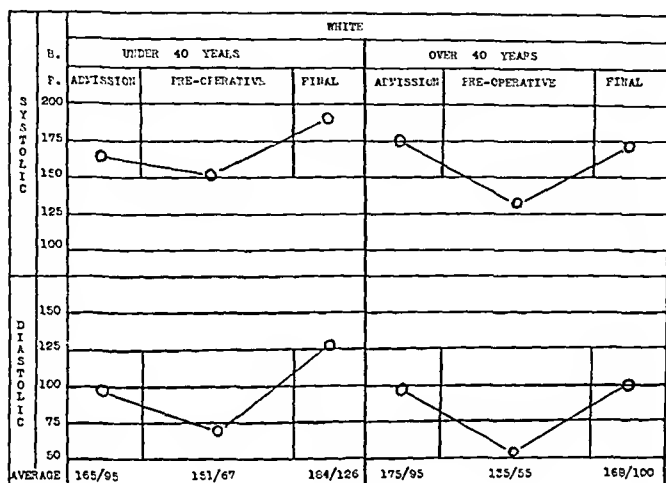


Chart 1.

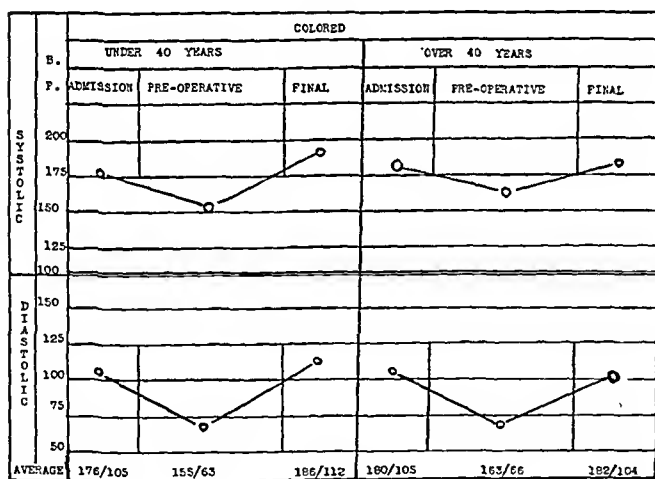


Chart 2.

Yet all of this does not give one the limitations of renal functions, and only a slight indication as to the extent of renal damage. It does not approach a means of estimating the gravity of such cases, the capacity of recuperative power of such damaged kidneys, or the risk involved. Under adverse circumstances one has a tendency to avoid great surgical risk primarily for the relief of pelvic pain, for in these cases one can expect only indirectly to relieve or improve the hypertension and myocardial damage, so we must conclude the risk is taken primarily for the relief of pelvic pain.

A study of the blood pressure over a period of time was informative. In both the white and colored patients the blood pressure levels before the age of 40 years were lower, the white being about 20 points lower than the colored; the greater fall in both systolic and diastolic pressures was noted in the colored with rest and treatment. This was probably due to the general systemic improvement in colored patients. In the final readings, taken from two to six years after operation, both groups under forty show a progressive rise in both systolic and diastolic pressures over that of preoperative findings (Charts 1 and 2).

In only five instances were there falls below the initial admission pressure, and these occurred in the group of patients under 40 years of age. Was this the result of the intervening years of increased activity, or previously impaired cardiovascular systems, or progressive changes in susceptible individuals? It does point out conclusively that, so far as fibroids and hypertension are concerned, nonspecific operations upon pelvic pathology do not permanently lower the blood pressure, nor does it seem to prevent its gradual expected rise in later years. From consideration of blood pressure alone, it seems that fibroids are only an associated finding, or fibroids would be found earlier in life and more frequently associated with hypertension. With proper handling, the risk in such cases is no greater than the average major pelvic operation by age grouping.

In patients over 40, the initial pressure was higher, the improvement from rest was greater in the white than in the colored group, but almost invariably the previous pressure returned or was slightly higher in both groups. This elevation began with activity of the patient and eight years after operation had not changed appreciably. Study of charts on blood pressure changes shows with age an increased incidence of hypertension, e.g., Gager¹ in a series of 500,000 life insurance examinations, reports:

YEARS	SYSTOLIC	DIASTOLIC
20-29	3.9%	3.4%
30-39	11.6%	8.9%
40-49	22.2%	27.0%
50-	36.7%	31.5%

As the average age of our group is 41 years, one would expect a certain percentage of rises in pressure to be associated with age.

Tables IV and V show the menstrual records of these patients. A predominant number of patients had regular periods, and in the colored race flooding was present in over 30 per cent. Colored patients frequently have given a history of bleeding for two years without treatment, have shown a hemoglobin of 35 per cent or less, and have presented no alarm over the condition.

Excessive menorrhoea should not be considered as evidence of a polyglandular state, but as a manifestation of a deficiency which results in a

TABLE IV. MENSTRUAL RECORD, WHITE

DURATION		REGU- LAR	IRREG- ULAR	MENO- PAUSE	FLOOD- ING	DIS- CHARGE	CLOTS	PAIN
Under 40 years	2	4	0	0	0	2	1	2
	4-5 days							
	2 5-7 days							
Over 40 years	1	2	0	0	1	0	1	2
	3-4 days							
	1 7-8 days							

TABLE V. MENSTRUAL RECORD, COLORED

DURATION		REGU- LAR	IRREG- ULAR	MENO- PAUSE	FLOOD- ING	CHARGE DIS-	CLOTS	PAIN
Under 40 years	75% 3-5 days	40	3	2	12	28	20	18
	17% 6 days							
	8% 10 days							
Over 40 years	12 none	35	6	12	16	32	23	21
	86% 3-5 days							
	2% over 6 days							

premature disintegration of the corpus luteum and consequently a hastening in the appearance of menstruation. This is substantiated in cases of fibroids where the growths produce mechanical and circulatory deficiencies of the endometrium and are associated with cystic follicular degeneration of the ovaries and fibrosis and early degenerative changes in corpora lutea. The commonest cause of profuse menses is due to some kind of interference with the mechanism which controls the flow of blood to the desquamating endometrium. Fibroids play a large part in the distortion of musculature, and disturb by congesting the pelvis and affecting ovarian secretion.

In 14 of the colored women, the menopause had taken place from six months to twelve years earlier. Previously these patients sought relief from incapacitation, caused by pelvic pain in most instances. The belief has long been held that once the menopause has begun fibroids will reduce and cause no further trouble. Frequently fibroids cause more pain after the menopause because of disturbances with adhesions than was complained of during active menstrual life; also, one should keep in mind the fact of malignant degeneration in growths after the menopause.

In this series, one white and 34 colored patients, or 33.6 per cent, had complete hysterectomy (Table VI); 5 white and 64 colored patients, or 66.3 per cent, had supravaginal hysterectomy with practically the same mortality (1.8 per cent); 37 had hysterectomy and salpingectomy without removal of ovaries. When possible, the tubes were left in place for better blood supply to the ovaries. Fifty-two had incidental appendectomy. Unless the appendix was definitely involved in old adhesions or there was evidence of pathology, it was deemed wise not to disturb it because of increase in the risk. It was not the time element in removal

TABLE VI. OPERATIONS

RACE	TYPE		TIME OF OPERATION	TYPE ANESTHESIA	IMMEDIATE RESULTS
White 6	Complete hysterectomy 1 Supravaginal hysterectomy 5	Bilateral salpingectomy 4 Bilateral oophorectomy 3 Appendectomy 4 Perineorrhaphy later 2	Shortest 1 hr. 15 min. Average 1 hr. 33 min. Longest 1 hr. 55 min.	Spinal 6	Improved 6
Colored 98	Complete hysterectomy 34 Supravaginal hysterectomy 64	Bilateral salpingectomy 25 Bilateral oophorectomy 33 Unilateral ooph. 26 Appendectomy 48 Perineorrhaphy 17	Shortest 35 min. Average 1 hr. 48 min. Longest 3 hr. 8 min.	Spinal 68 Local 3 Gas oxygen 2 Cyclopropane ether 21 Ether 4	Improved 94 Died 4

of an incidental appendix, but the additional disturbance of another system which might prove too heavy a load for a bad risk patient.

Perineorrhaphies were done in 19 patients. We felt that this was important in this particular group of cases, and the procedure was usually carried out after the major operative work had been completed without prolongation of anesthesia.

Regardless of common belief, time consumed at operation is an important element in these cases and our set-up with the Louisville City Hospital is such that severe cases are the ones operated upon by the visiting staff and the time element, never to the detriment of accuracy, is one to be observed. The average time for all cases was one hour and forty minutes; in some of the more critical cases only thirty-five minutes was necessary for a complete hysterectomy.

The type of anesthesia is an important factor. At first these patients were conditioned for an average period of ten days, and low spinal anesthetics were given. Seventy-four of the 104 cases were done under spinal anesthesia under the supervision of the Department of Anesthesia.

Deaths were as follows:

- 1, spinal anesthesia, pulmonary edema (two weeks postoperative, second closure).
- 1, spinal anesthesia, bronchopneumonia, three days postoperative.
- 1, local anesthesia, nephritis and uremia, ten days after.
- 1, cyclopropane anesthesia, cerebral hemorrhage, and cardiovascular disease.

The disturbing factors were, in spite of carefully prepared patients and low spinals with small dosages, that these cases with hypertension

would have a marked drop in blood pressure which could not be controlled by synephrine or adrenalin, or coramine, and in some cases would have a very slow return of pressure to normal. This was followed usually by a disturbance in urinary output, which is to say the least quite disturbing for a few days, but with forced glucose intravenously, and other supportive therapy the kidney function gradually returned to the previous levels. For these reasons we have been trying to adapt the anesthesia to the patient, rather than the patient to the anesthesia, and have used more inhalation anesthesia of late which can be more completely controlled. This has not been entirely satisfactory, for in these large growths relaxation is important for exposure and removal of the tumor. Our present regime is a combination of cyclopropane with ether only for a short period of relaxation in the deep phase of the anesthesia.

TABLE VII

HOSPITAL DAYS				POSTOPERATIVE COMPLICATIONS	
WHITE		COLORED		COLORED	
Under 40 years	Lowest	21 days	Lowest	16 days	2 Wound infections and transfusion
	Average	24 days	Average	24 days	1 Shock and transfusion
	Highest	28 days	Highest	50 days	1 Infected wound, secondary closure
Over 40 years	Lowest	21 days	Lowest	9 days	2 Shock and transfusion
	Average	24 days	Average	23 days	2 Wound infections
	Highest	27 days	Highest	59 days	1 Pyelitis
					1 Bronchopneumonia
					2 Upper respiratory infections (mild)
					1 Cardiac failure, responded to digitalis
					1 Wound infection, strep. peritonitis, pulmonary edema
					1 Toxic nephritis and uremia
					1 Metastasis papillary adenocarcinoma

With an average preoperative preparation of ten days (Table VII), these patients had average hospitalization of only twenty-four days, and a surprisingly smooth convalescence, the lowest 16 days, and the longest 73 days. Major complications included: 6 wound infections with 2 necessitating secondary wound closure, 3 cases treated for shock, 1 death from bronchopneumonia, 2 other slight upper respiratory infections, 1 acute cardiac failure which responded to digitalis therapy, and 1 uremia. Seventy-five per cent of the complications appeared in the over 40-year-old colored group and the convalescence in this group was slower.

A study of the pathology reports is illuminating. All patients had multiple fibroids; they were studied only to rule out malignancy, which was found in only one patient (microscopically), and was not considered clinically important. That patient is living and well four years postoperatively.

Our cases were grouped clinically as to phase of menstrual cycle patient was in at time of operation, by ascertaining the cycle, and then taking the date of last menstrual period and estimating what phase the endometrium should be in, grouping into:

1. Premenstrual
2. Menstrual; or those bleeding at time of operation, or calculated to be at menstrual period
3. Postmenstrual
4. Menopause

With this clinical grouping we studied only the cases which had ovarian and endometrial pathologic findings (Tables VIII, IX, and X). Our conservatism makes our material small for this group. Thirty-seven patients did not have the ovaries removed. We believe this conservatism was of great advantage to the patient even if a loss to science.

We believe that the monthly proliferative changes in the endometrium are based on follicle activity, and that secretory and premenstrual changes are due to the corpus luteum activity. The amount of hormone

TABLE VIII. WHITE

CLINICAL PHASE		AGE	ENDOMETRIAL PATH. REPORT	OVARIAN PATH. REPORT
Under 40 years	Premenstrual 2	37 yr.	1 Premenstrual endometrium secretory 1 Atrophic endometrium Chronic endometritis	1 Retention follicle cyst Corpora albicantia 1 Retention follicle cysts Fibrosis
Over 40 years	Menstrual 1 Postmenstrual 1	48 yr.	1 Polypoid hyperplasia 1 Polypoid hyperplasia	1 Fibrosed with follicle cysts 1 Fibrosed with follicle cysts

TABLE IX. COLORED PATIENTS, UNDER 40 YEARS

CLINICAL PHASE	AGE YR.	ENDOMETRIAL PATH. REPORT	OVARIAN PATH. REPORT
Premenstrual 6	35.4	3 Hyperplastic endometritis 2 Early interval endometrium (nonsecretory) 1 Chronic atrophic endometritis	3 Retention cysts with corpus luteum cysts and fibrosis 1 Papillary cystadenoma (benign) 1 Corpus luteum cyst 1 Atrophic ovary
Menstrual 5	35	5 Chronic hyperplastic endometritis	1 Granulosa cell tumor 3 Retention follicle cysts 1 Fibrosed ovary
Postmenstrual 12	35	9 Hyperplastic polypoid endometrium with lymph. infiltration 3 Late interval endometrium	6 Retention follicle cysts with corpus luteum 3 Retention follicle cysts 2 Fibrosed ovaries 1 Ovarian abscess
Menopause 4 6 mo.-2 yr.	36	2 Hyperplastic endometritis 1 Atrophic endometrium 1 Premenstrual endometrium	2 Fibrosed ovaries with retention follicle cysts and corpus luteum cysts 1 Fibrosed ovary, no cysts 1 Retention follicle cysts

will determine, in a sense, the amount of reaction (or secretion) shown in the endometrium; increased follicular activity will lead to increased growth of endometrium.

TABLE X. COLORED PATIENTS, OVER 40 YEARS

CLINICAL PHASES	AGE YR.	ENDOMETRIAL PATH. REPORTS	OVARIAN PATH. REPORTS
Premenstrual 12	43.5	4 Fibrosed endometrium 7 Polypoid hyperplastic endometrium 1 Premenstrual (nonsecretory)	11 Retention follicle cysts with fibrosis of ovary 1 Retention follicle cyst and corpus luteum
Menstrual 5	44.5	3 Chronic endometritis 1 Atrophic endometritis 1 Early menstrual (secretory)	1 Papillary cystadenoma 1 Bilateral dermoid cyst 2 Retention follicular cyst 1 Retention follicle cyst, degenerated luteum cyst
Postmenstrual 10	46	5 Atrophic endometritis 4 Polypoid hyperplastic endometrium 1 Late interval endometrium	5 Retention follicle cysts with fibrosis 4 Retention follicle cysts with corpus luteum 1 Retention follicle cyst
Menopause 8 6 mo.-12 yr.	52.7	4 Polypoid hyperplastic endometrium 3 Atrophic endometritis 1 Adenocarcinoma (fundus)	6 Retention follicle cysts with fibrosis 1 Calcified dermoid ovary 1 Adenocarcinoma metastasis

Analysis of the findings, as is shown in Tables VIII, IX, and X, permits the following conclusions: (1) A woman can bleed from any type of endometrium. (2) Polypoid hyperplasia of endometrium is seen with retention follicular cysts of the ovaries, with or without luteal cysts. The predominant finding is that 64 per cent of fibroids have corpus luteum cysts. (3) Chronic endometritis with retention cysts of ovaries is evidence of old pelvic infections. (4) Atrophic endometritis with follicle retention cysts and ovarian fibrosis are seldom associated with corpus luteum cysts. (5) The unusual findings in this small, unselected group were dermoids, papillary cystadenoma and granulosa cell tumor and carcinoma of fundus.

In 14 of the cases which were from six months to twelve years postmenstrual, as decided by cessation of bleeding and not by age, the fibroid growths continued with symptoms which incapacitated the individual. Persistent symptoms with abdominal growths after the menopause suggest possible malignant changes and we believe warrant surgery.

In 3, or 21.4 per cent, of these postmenopausal cases, secretory changes were found in the endometrium. It has definitely been proved that follicle growth and even ovulation with corpus luteum formation occurs months or even years after the menopause. This fact should make us more conservative about oophorectomies.

Endometrial studies indicate that ovarian activity may revive spontaneously and lead to periods of bleeding. Such a finding should not

lessen our vigilance for carcinoma. Briepohl,³ in 130 cases of post-menstrual bleeding, found a stage of proliferation in 10 per cent and a secretory phase in 2.3 per cent, a hyperplasia of the endometrium in 11.5 per cent, all of which indicate a stimulation of the endometrium by ovarian hormones after menopause. This demonstrates that the ovaries may be re-activated and that the endometrium itself may respond after it has become atrophic, and that both have functional possibilities after the menopause and should not be promiscuously removed.

TABLE XI. CAUSES OF DEATHS

UNDER 40 YEARS		OVER 40 YEARS	
<i>Hospital Deaths</i>		<i>Hospital Deaths</i>	
1 Nephritis and uremia		1 Bronchopneumonia	
		1 Nephritic toxemia	
		1 Pulmonary edema (2 wk. secondary closure)	
<i>Under One Year</i>		<i>Under One Year</i>	
1 Heart failure		1 Cardiovascular disease	
<i>Under Two Years</i>		1 Myocarditis	
1 Cardiovascular disease		1 Heart failure	
		1 Lobar pneumonia	
		1 Cancer fundus uteri	
<i>Two to Six Years</i>		<i>Two to Six Years</i>	
1 Cardiovascular disease		1 Heart failure	
1 Pulmonary tuberculosis		1 Stroke	
1 Stab wound shoulder, pneumonia		1 Cerebral hemorrhage	
1 (White) Cardiovascular disease		1 Fracture of vertebra, cord lesion	
		1 Carcinoma cervix	

Causes of deaths are given in Table XI. Salvage of the group is shown in Table XII, with hospital death rate of 3.8 per cent and a total eight-year mortality of 19.2 per cent. We feel that we have restored a debilitated, greatly handicapped group to greater capacity.

TABLE XII

	WHITE			COLORED					TOTAL MOR-TALITY
	LIVING AND WELL	RELIEF	DEATHS UNDER 2 YR.	LIVING AND WELL	RELIEF	HOSP. DEATHS	DEATHS UNDER 2 YR.	DEATHS 2-6 YR.	
Under 40 years	2	2	1 H.C. V.D.	25	13	1 1.02%	2 2.04%	4 4.08%	7.6%
Over 40 years	1	1	0	35	6	3 3.06%	4 4.08%	5 5.1%	11.5%
						Total 3.8%			Total 19.2%

Let us look into the rehabilitation of this group (Table XII). In the white patients we have one dead, 50 per cent working and 50 per cent on relief but comfortable, and able to be about better than before. In the colored we have 65 working and apparently well for years, 19 on relief and definitely subjectively relieved. Some are incapacitated by progression of heart condition. Only 3 of these may be classified as hopeless at present.

Many of these cases have been seen from time to time in the clinical follow-up over years. In the final follow-up of these cases, all are accounted for. Four were heard from in other states and not directly checked. There were 5 special clinics held in which 65 per cent of the patients were seen. The deaths and their causes were checked through the Bureau of Vital Statistics of Kentucky State Board of Health, and those living and on relief were checked through the Municipal Bureau and Family Service Organizations, and some of those unable to come in for observation were contacted in their homes. This phase of the study alone was very exhaustive, but most instructive.

SUMMARY

1. Presentation of 104 cases of uterine fibroids with hypertension, which were studied from two to eight years after operation.

2. Presentation of effects of rest on blood pressure, and showing that it is not materially affected by operation, nor does operation prevent its later rise.

3. Comparative study of symptoms, findings before and after forty years of age with deductions.

4. Detailed study of endometrium and ovaries in cases where removed in relation to clinical cycle of menstruation and discussion, showing that in 21 per cent of cases after menopause there is evidence of continued ovarian function.

5. Causes of deaths given at different periods after operation.

6. Mortality and salvage in this series show that these cases when handled properly do not have greater mortality than the average major pelvic operations for age grouping, with satisfactory salvage.

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908 BROWN BUILDING

DISCUSSION

DR. PAUL TITUS, PITTSBURGH, PA.—An important point perhaps was lost in the figures: Dr. Johnson's emphasis that perineal repair should be done when indicated in addition to the operation for fibromyomas. Out of this large group of fibroids, 13 per cent showed hypertension. Does this mean that fibromyomas tend to cause hypertension? I think Dr. Johnson wants to indicate to us that it should not be given such interpretation. He said that blood pressure and cardiorenal conditions are not disturbed, favorably or otherwise, by fibromyomas. I should like him to clarify that point.

Did I understand Dr. Johnson to state that hypertension complicating fibromyomas as an added risk may be discounted? It seemed to me that the mortality rate of the patients with hypertension was higher than that of the average group of patients undergoing operation.

DR. WILLIAM T. MCCONNELL, LOUISVILLE, KY.—Dr. Johnson and I have worked together for many years, and I am familiar with this particular series of cases. This does not represent a cross section of cases dealing with fibromas per se. This series he has reported is a study of the possibilities of salvage of the old "crock." There is no intelligence in their seeking health but they come because they are in pain, and they are in a very bad physical condition. It takes skill and courage to tackle these cases. This report covers the possibility of rehabilitation of a class of patients who are a burden to society and a misery to themselves. The paper shows to me what can be done in the matter of relieving suffering and a certain amount of economic strain on the body politic.

DR. F. S. WETHERELL, SYRACUSE, N. Y.—I would like to have Dr. Johnson clarify the matter of hypertension in relation to hysterectomy for fibroids.

DR. JAMES E. KING, BUFFALO, N. Y.—The mortality of hysterectomy in itself is not to be feared today, because we have repeated instances of reports of cases, 300, 400, 500, 600, without a death. In my own series I have had 530 consecutive hysterectomies without a death. In that number, of course, were a considerable number of hypertensive cases. In my own work I have drawn an arbitrary line which indicates when I am dealing with a case which is possibly going to give trouble. Any woman who has a blood pressure of 170 or above I regard with considerable anxiety.

A few years ago I analyzed 537 patients upon whom I had performed a hysterectomy, and of that number 65.7 per cent had a blood pressure of 120 to 170 systolic. These do not worry me. But 8.6 per cent of the 537 patients had a blood pressure of 170 to 220. Now that 8.6 per cent did worry me. With a more careful selection of the anesthesia, we are not in the same position that we were a few years ago when ether was generally used.

I would like to know whether Dr. Johnson has any particular line of procedure in preparing his patients for hysterectomies? I think his mortality was a little high for the present day, but I presume the average Negress is not altogether a very suitable person for any type of abdominal surgery.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—Dr. Johnson is dealing with a type of fibromyoma and a type of patient with which we are all familiar in the South. Neither the patients nor the fibromyomas are like those encountered among the general population of New York or Pennsylvania. For the type of case with which Dr. Johnson is dealing, his mortality is definitely low, for I know that in many hospitals the mortality in such cases has run from 6 to 10 per cent.

I once spent ten years in studying the blood pressures in such cases before and after operation and concluded that hypertension was not essentially a very serious factor of this type of operation.

DR. WALTER T. DANNREUTHER, NEW YORK, N. Y.—After a modest experience with hysterectomy extending over a good many years, I have come to the conclusion that hypertension per se is of little consequence. The essential factors are the associated obesity, renal damage, compromised myocardium, or impaired metabolism.

The important therapeutic items, which can be carried out with derelicts as well as with other women, are careful preoperative study and preparation of all patients.

I also believe that cyclopropane anesthesia, given by an expert, and an expeditious operator are additional important factors of safety, in patients who are relatively poor risks.

DR. JOHNSON (closing).—My purpose in this paper was to present the findings in a group of cases and analyze the results to see whether the surgical risk, money expended by the hospital, and salvage of cases justified continuation of this work. These patients were relief cases from the Work House, Poor People's Home, and Home of the Invalids. The procedure was carried out with the hope of offering them relief from discomfort and for possible rehabilitation.

In these cases, we operated principally for pelvic pain, and no attempt was made to consider or prove the relationship between the fibroids and hypertension. This association was mentioned because it is frequently found in such bad risk cases. I tried to point out, however, that nonspecific operations on the pelvis had no effect upon lowering of the blood pressure, and apparently do not prevent its subsequent rise in later years.

All patients were carefully prepared from a medical viewpoint, with rest, diet, digitalis and other measures as indicated, for an average of ten days before operation. The determination as to the optimum time for operation requires the greatest consideration and care.

Dr. Titus has stated that 10 per cent of cases of fibroids have hypertension. I did not wish to infer that a certain percentage of fibroids had hypertension, but simply wished to state that about one case in every seven admissions of fibroids had hypertension, and that 18 cases of our series had relaxed vaginal outlets which, we feel, it is important to repair in association with or following hysterectomy.

In these cases, mortality records cannot be considered, but from an analysis of this series over a period of eight years, we feel it is worth while operating upon them for the relief of pain, that the mortality rate is not prohibitive, that the salvage is satisfactory, and renders an apparently hopeless invalid who is on relief, comfort and at least a 60 per cent chance of earning a livelihood.

PATHOLOGY OF THE EMBRYO AND ABORTION

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THE accumulating results of studies of spontaneously aborted products of conception seem to necessitate a revision of our approach to the clinical problems involved.

It is conceded that at least 10 per cent of all pregnancies end in spontaneous abortion.^{1, 2} Of these something approaching 90 per cent disclose pathology of the conceptus absolutely or relatively incompatible with a continuing pregnancy.³ In the former early death of the embryo results; in the latter the embryo in spite of pathology may continue to grow with resultant gross fetal defects, monsters, hydrocephalus, spina bifida, etc., a potential 12 per cent according to Mall.⁴

¹Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

The etiology may be intrinsic in the sense of male or female germ plasm defects or in defective cell union. The trophoblast may fail to establish itself normally, due to endometrial faults, histologic or functional, any of which may prevent or interfere with a subsequent development of the embryo proper. If death of the embryo occurs early, an atypical growth of the chorion may continue as a cystic degeneration.

Storch⁵ reported this in 1878 and estimated its incidence as 75 per cent. Hertig³ found it in 66.9 per cent of the material he has studied and suggests that this early cystic degeneration is a potential first phase of the true mole the invasive type of which in turn, as Phancuf⁶ has described, is the genesis of chorionepithelioma.

Early cystic degeneration is so common, a true mole so rare, the correctness of Hertig's contention seems questionable. If it were correct, the early expulsion of this defective ovum would appear as an important defense mechanism.

When an abortion actually occurs, post facto findings indicate we were most frequently dealing with the terminal phase of an inevitable process, the end result of an already interrupted pregnancy. In no correct sense can any part of the clinical picture be designated as a threatened abortion. Streeter⁷ has further emphasized the important fact that death of the embryo usually precedes by several weeks, its eventual expulsion.

Besides this early pathology, there are encountered various disorders (anatomic anomalies and malpositions) of the placenta. Hertig³ in his series found a 9 per cent low implantation, confirming our clinical suspicion that a definite number of abortions are in reality early placenta previas.

In the abortion which has this definite background of pathology, attempts to prevent expulsion would obviously be ill advised, perhaps unsafe, eventually futile. Its urgent clinical problems are in its complications: incompleteness, hemorrhage, and sepsis.

The clinician's difficulties, however, are not limited to these cases *with the definite pathology* which abort, for he encounters a considerable group of patients having symptoms indicating the possibility of abortion but in which it may or may not occur. If it does occur, the percentage probabilities indicate pathology of the conceptus, but it may belong to that 10 per cent which histologically shows only the usual hemorrhage, evidences of infection, inflammation and necrotic changes. One's impression is that these cases are quite numerous but a tabulation of 500 consecutive cases delivered at term in the Booth Hospital disclosed only a 3.8 per cent incidence of early pregnancy staining or bleeding.

What happens in the patient not aborting is conjectural. A partial disturbance of placental attachment may be a reasonable hypothesis.

Some intercurrent interference with an otherwise normal pregnancy with a further deduction that a not too extensive primary process may permit regeneration and repair. To delay expulsion until this process of repair can establish itself is most important.



Fig. 1.—Cystic degeneration of the chorion from a defective ovum, forty-six days after the onset of pregnancy, showing a portion of the wall of the chorionic sac, with scattered villi lying near by. The chorionic sac is bordered externally by a narrow uninterrupted syncytium which lies on a layer, varying in thickness, of loose connective tissue showing here and there large and smaller poorly delimited cystlike accumulations of fluid. There are few lacunae-like endothelial-lined spaces containing the remnants of disintegrating nucleated red blood cells. This chorionic sac is lined internally by a somewhat smaller thin-walled sac lined by flattened out squamous-like cells. This latter layer of cells formed the inner wall of the whole sac.

The villi are comparatively few in number and unusually simple in design. They are coarse, bulky, and show little tendency toward branching. The stroma is both absolutely and relatively increased in proportion to the bordering trophoblastic layer. (X14.)

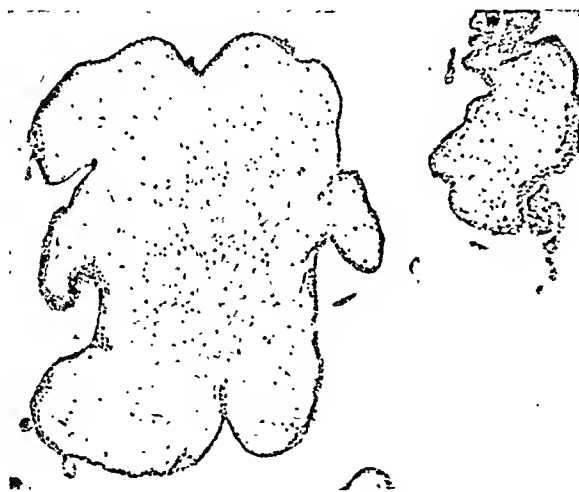


Fig. 2.—A higher power of one of the villi shown in Fig. 1, simple in design, poorly differentiated lacks well-developed branching processes, and instead shows only few protruding buds. The stroma is distended and edematous, showing clear spaces filled with fluid. The intercellular fluid lacks any tinctorial reactions. The stroma is composed of spindle and spiderlike cells whose processes join one another. In this, no vessels are clearly demonstrable, and in this villus there are no developing red blood cells. The edematous stroma is bordered by a thin and inconspicuous trophoblastic wall. Only at two points is there a slight tendency toward syncytial budding. (X76.)

In the light of present knowledge it seems then that we have two major premises.

First: The clinical picture of an abortion may, and most commonly does, represent the expulsion of a defective (already dead) ovum. Any



Fig. 3.



Fig. 4.

Fig. 3.—A still higher magnification of portion of villus seen in Fig. 1, showing the limiting trophoblastic wall, and its sharp separation from the underlying edematous stroma. Here the syncytium and Langhan's layer of cells may be clearly separated. The syncytium is orderly. There is a well-developed brush-border, the relative ratio of nuclei to cytoplasm favors the latter. The nuclei are uniform in size, shape, and staining; in places they are clumped. The Langhan's layer forms a continuous and monotonously uniform line of cells beneath the syncytium. These cells have pyknotic nuclei, their cytoplasm is clear and vacuolated. No mitoses are seen. The picture is one of hypoplasia. ($\times 600$.)

Fig. 4.—Defective embryo, 8 weeks, sac discharged intact, showing a sac bordered by a rather sparse zone of chorionic villi. Within the sac is only a single small nest of cells. This was loosely adherent to the inner surface of the cyst by a delicate transparent threadlike stalk. ($\times 6$.)

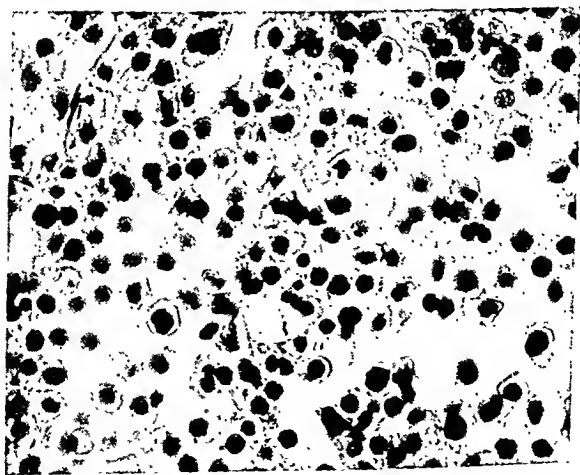


Fig. 5.—A high-power magnification of the small nodule found within the cyst, shown in Fig. 4. This small nest is almost entirely composed of developing red blood cells that lie within distended lacunar spaces. This island of erythropoietic tissue was the only remnant of embryonic tissue present. ($\times 640$.)

attempt to prevent its expulsion, if not actually harmful, serves no useful purpose.

Second: There may be an intercurrent disturbance of an otherwise normal pregnancy, a true threatened abortion, exact opposite of the first mentioned premise, in that every effort to prevent expulsion is required.

From this derives an urgent clinical need, the ability to determine in advance of the eventuality with which group we deal in a given case. If practice would keep step with scientific progress to avoid treatment absurdities, it must set up clinical criteria for this differential diagnosis. Toward this end we have something of a start. For instance, on a percentage basis most of the irreparable pathology will be encountered in the early abortions. Excessive and prolonged bleeding is significant. Temperature elevation is almost pathognomonic of a terminated pregnancy.

The treatment of abortion is not germane to the subject of this communication but certain of its aspects are pertinent. The testimony of a voluminous and enthusiastic literature as well as common observation indicates that present-day therapy centers largely in the use of corpus luteum hormone and in the administration of vitamin E though candor may compel us to admit that much of it seems hardly more than testimonial evidence.

Concerning vitamin E, advocated originally for habitual abortion,⁸ it is now very generally employed in the treatment of any abortion. There are probably few patients today beginning to bleed during early pregnancy, who do not get wheat germ oil. Without consuming any time analyzing the reasoning involved, it might suffice to say that if vitamin E deficiency plays much part in the cause of abortion, we would have had considerable opportunity in clinical observation to realize that fact. I refer to the severe nausea and vomiting cases. Here there is of necessity a marked deficiency in vitamin E intake, along with everything else, and yet about the only thing these patients *never do* is to abort spontaneously.

The common reason for the employment of hormones is as substitution therapy. It is very obvious that a progesterone deficiency may play a background part in some pathology of the ovum,⁹ the abnormal endometrium, faulty nidation, failure of the trophoblast sequence, but if so, it represents a fait accompli, long before the clinician begins to deal with the abortion.

A function, more correctly perhaps, an attribute of progesterone, has been described by Falls¹⁰ and others, whose experiments indicate its inhibiting effect on uterine contractions. This would seem the rationale of its use in threatened abortion but, and important, a *very definite contraindication* for its use in the woman expelling a pathologic ovum. On the other hand, Kurzrok¹¹ reports increased uterine contractibility

following its administration, and Hamblen¹² has recently introduced another disconcerting note, suggesting that large doses of progesterone, by interfering with intrinsic progestin metabolism may precipitate abortion. He further suggests that its administration may also interfere with therapy in thyroid dysfunction, the importance of the latter already having been emphasized by Litzenberg,¹³ Bloss,¹⁴ and many others.

It would seem, from the conflicting evidence, that the value of the corpus luteum hormone in the treatment of abortion is still an open question.

CONCLUSIONS

In the light of present knowledge, the clinician is justified in concluding:

1. That most spontaneous abortions occur as a result of pathology of the conceptus incompatible with continuing pregnancy and that the clinical picture of abortion here represents in reality a terminal phase of an already interrupted pregnancy.

2. That a smaller group is encountered in which some intercurrent "accidental" type of pathology develops in an otherwise normal pregnancy, in which abortion may or may not result, and to which the clinical term "threatened abortion" correctly applies.

3. That intelligent management of abortion requires first a differential diagnosis, determination in advance to which group a given case belongs.

4. That in the treatment of "threatened abortion" there should be no question of the safety of any therapy employed and at least, a reasonably understandable justification for its use.

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80 BAY STATE ROAD

DISCUSSION

DR. FREDERICK J. LYNCH, BOSTON, MASS. (By Invitation).—A discussion of the pathology of the embryo and spontaneous abortion usually includes a consideration of the condition from the point of view of the fertilized ovum, a disturbance of the endocrine or vitamin balance and a local or systemic derangement of the maternal organism.

Concerning the ovum, the most complete and comprehensive work has been done by Hertig and his associates of Boston, who have approached the subject from the viewpoint of the pathologist. They classify two groups: namely, the pathologic and nonpathologic ova, the former being those ova in which no embryo is found or in which it is extremely defective. Nonpathologic ova include those in which normal embryos are found, or in which an embryo is present with deformities which would not interfere with the development of the fetus to full term.

More than one-half of the pathologic ova spontaneously aborted showed evidence of early hydatidiform degeneration of the chorionic villi. These hydatid changes were also found in the nonpathologic ova but to a much less extent, 10 per cent (11.6). Hertig states that the cystic degeneration of the chorionic villi is due to a failure of the vessels of the chorion, which develop independently of the embryo, to anastomose with the circulation of the fetus, as a result either of the absence of the fetus or of its extreme defectiveness. The activity of the chorionic epithelium results in a collection of fluid in the loose tissue of the chorionic villus from which it is not withdrawn, if the fetal circulation is nonexistent or if it fails, and a hydatidiform degeneration results.

The lessened occurrence of hydatidiform deterioration in nonpathologic ova, spontaneously aborted, is explained by the fact that the fetal circulation has, at least, functioned for some weeks. If the usual spontaneous abortion fails to occur, these ova may continue to develop and give rise to the typical mole.

Obviously in this type of case, as Dr. Paine states, the treatment should consist of helping the uterus expel its potentially harmful contents, rather than the usual attempts to allay these efforts. Unfortunately at the present time this condition cannot be detected clinically; indeed it can only be determined microscopically, in most of the early cases, after expulsion of the uterine contents.

In the nonpathological ovum, bleeding frequently does not appear until after the death of the embryo and the abortion is incomplete. Much time and effort are spent trying to nurture a terminated pregnancy and frequently considerable expense is incurred by the futile administration of expensive hormones. Again, if the diagnosis could be accurately made that the abortion was incomplete, our efforts could be intelligently directed toward encouraging and aiding the uterus to empty itself.

An expectant policy, combined at times with endocrine or vitamin therapy, is the usual manner of handling a threatened spontaneous abortion. The present criterion for the diagnosis of incomplete abortion, in addition to the signs mentioned, namely excessive bleeding, and temperature, is the presence of fetal tissue in the dilated cervical os.

Some work is being done in an attempt to make the early diagnosis of incomplete abortion from the vaginal smear. In the vaginal epithelial cells there are observed definite changes which reflect different events that are taking place in other parts of the female generative tract. It is well known that during pregnancy there is a marked piling up or cornification of the vaginal epithelium. With the advent of parturition, there is a marked desquamation of these epithelial cells, to the point that basal cells, or pavement membrane cells, with their characteristic appearance and staining qualities appear in considerable numbers in the smears. As these cells are found only in smears from postpartal and postabortal patients (Fletcher), it is felt that their presence in a case of questionable incomplete abortion might be accepted as indicative of this condition.

Admitting that the average patient confronted with the possibility of a spontaneous abortion would frequently prefer to wait until the ovum is partially expelled from the uterus before abandoning hope and permitting active measures to be taken to empty the uterus, the possible information derived from the smear would, at least, be of prognostic value.

It seems quite probable that some ova, from normally fertile women, are defective. Thus, if the life span of a normal ovum is forty-eight hours, the thought has been brought forward that fertilization in the last hours of this period may result in the fecundation of an imperfect ovum, with a consequent spontaneous termination of the pregnancy.

It also may be mentioned that possibly imperfect or damaged spermatozoa may succeed in fertilizing normal ova, in spite of the common chemical as well as mechanical attempts at contraception. It may happen that this union of a normal ovum and a faulty spermatozoon can be a further cause of defective pregnancy and resultant spontaneous abortion.

DR. JOHN G. WALSH, PROVIDENCE, R. I.—The most important of the varied causes of spontaneous abortion, those due to embryonic defects, has been stressed by Dr. Paine, and he has emphasized the futility of attempting any form of therapy that might prevent the expulsion of a defective ovum. It is very doubtful, however, that with any form of therapy we can prevent the expulsion of such a grossly deformed early fetus.

In any large series of abortions, there are many whose cause cannot be accurately appraised in the present state of our knowledge. We have all seen successive pregnancies result in abortion, where we have felt that the factors involved were wholly accidental. Again we see women with repeated spontaneous abortions in whom there must be a recurrent maternal factor. Malpas has estimated that such a factor is present in at least 1 per cent of all pregnant women. Irving was unable to assign a cause in 8.5 per cent of his series.

It is probable that nearly one-half of the threatened abortions will be saved by bed rest and the milder forms of sedation. Our main concern in treating such cases is to prevent uterine contractions or to allay them if they have already begun. The use of extracts of corpus luteum appears to have been more successful than any other previously available method of treatment. Falls has shown that morphia may increase rather than allay uterine irritability.

Falls and his co-workers have also shown that it is possible to determine in about 95 per cent of cases whether the fetus is still alive at the time or shortly after the patient comes under observation. If we avail ourselves of this means of diagnosis, our treatment will not have the futility that Dr. Paine implies.

Dr. Paine's skepticism regarding the value of corpus luteum extracts may be justified in view of Hamblen's recent findings. There are, however, an increasingly large number of careful studies, reporting the successful use of progesterone in recurrent abortion.

DR. JAMES R. BLOSS, HUNTINGTON, W. VA.—In the last fifteen months we have had in our private practice 34 abortions, of which 19 were the so-called spontaneous type. Of these the metabolism readings were minus in 11, plus in 2, and normal in 1. In 5 it was not possible to run a metabolism before they had aborted.

The interesting thing is that the development of these fetuses is only continued to about six weeks. The average time of abortion in those with minus tests as estimated from the last menstrual period was 14.6 weeks. In those who were minus and on thyroid therapy (11 patients), the average was 15.8 weeks. Those with high metabolic rates averaged 14.3 weeks. Those in which no test was made averaged 12.5 weeks.

There must be a deficiency in the germinal cells which has an influence in producing an abnormal child. In this respect there came under my observation, some years ago, one very interesting family with a recurring anatomic abnormality. This young couple had had two children neither of which had a pyloric opening of the stomach. It is interesting that this young man's mother had one child with the

same type of abnormality. He had a brother whose wife had been pregnant twice and each of these children presented anatomic abnormalities.

The place to start with the prevention of abortions is not after pregnancy has commenced. When examining these cases do not neglect a study of the husband, because there will be found a number of such instances in which the wife will be normal and the husband discovered to be a hypoeudocrine. By treating him and securing normal spermatozoa, a successful pregnancy is secured. Several instances of this have been noted in our experience.

DR. EVAN SHUTE, LONDON, CANADA.—Mall and Meyer have been largely responsible for the opinion so widely held that most aborting embryos are abnormally constituted and that it is not advisable, therefore, to prevent their loss. Their extensive investigations were carried out about thirty years ago on specimens sent to them by physicians in the United States, Canada, and abroad. It is doubtful if these embryos represented random sampling, for only grossly abnormal formations would attract the interest of practicing physicians and be sent for study. Moreover, when we analyze the work of this famous team we find that of the first 1,200 accessions to their collection fully 353 were abnormal in structure. But only 244 of these 353 revealed embryos of any sort and, as 17 of these were in tubal pregnancies, only 227, or 19 per cent, represented deformed embryos obtained from the uterus. In short, contrary to the usual impression, it is questionable if their studies support the contention that a *random* sampling of aborted embryos would reveal a majority, or even any very high proportion, of congenital anomalies.

Only recently has the profession possessed effective agents, such as vitamin E or progesterone, with which to combat threatened abortions. All of the literature since the war has not been accessible to me, but of 224 cases reported as threatened abortion or threatened miscarriage, 184 went on under such treatment to produce living children. Of these only 6, or 3 per cent, revealed anomalies of structure. This series of 184 includes 68 of my own cases, showing three defectives, an anencephalic, a congenital heart, and a large hemangioma on the back. I also have a letter from Dr. McGonigle, the first Englishman to use vitamin E extensively in such cases, in which he mentions "about a hundred" of them with no congenital deformities ensuing. The figure of 3 per cent of anomalies in the offspring is too low to justify a *laissez-faire* policy in treating threatened abortion.

I had the privilege three years ago of discussing a paper on placenta previa read by Dr. Greenhill before this Society. At that time I mentioned that we were collecting, very tediously, a series of case histories of women who had borne previously only congenitally deformed infants. These women were treated with vitamin E, either just prior to conception or immediately thereafter, in subsequent pregnancies. Wherever possible, their husbands were also given vitamin E prior to the conception, bearing in mind the remarkable ability of vitamin E to improve deficient sperm production and quality within ten to fourteen days. The series is still too small to warrant any conclusions, but it is mentioned at this juncture for its suggestive value. We now have ten such women who have been delivered of one to three infants since the defectives were born and four more such women as yet undelivered. Of the 12 children born of these 10 mothers since the birth of the defectives, 9 have been normal. The exact data will be published later. It at least suggests that we should not throw up our hands in despair before one of the most appalling phenomena in obstetrics.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—Dr. Paine's viewpoint would certainly simplify the teaching of the management of abortion. In the first place, apparently abortions are all due to defective embryos; and, in the second place, there is nothing you can do about it.

When I first used corpus luteum clinically I had difficulty in believing the apparent effects. I could not understand how a woman two to four months pregnant who had been having uterine contractions could, with an injection of a small amount of progesterone, suddenly have a cessation of uterine contractions, a cessation of the bleeding, and a continuation of the pregnancy. It was not until I put a bag in the uterus of a woman seven days postpartum, and produced good uterine contractions with pituitrin and saw these contractions stop a few minutes after using rabbit unit doses of an oily extract of corpus luteum, that I knew I had not been mistaken in my clinical observations.

When we had 41 cases studied clinically we reported them. In these 41 patients 87 per cent carried babies through to maturity and were delivered of normal babies. These women had previously lost 85 per cent of their pregnancies. One of my associates has been extending this work at the County Hospital, and we now have in a series soon to be reported about 400 cases. The percentage of recovery remains the same as in the smaller group.

Another significant fact that appeared very early in our study was that if the baby was dead in the uterus it would be expelled whether these preparations were injected or not. Also these injections will not influence uterine contractions if the woman is in labor.

As a control for this series we now have about 50 cases at the County Hospital observed within the last few months in which we have not been using the corpus luteum extract. We have allowed the patients to go along without the use of this preparation. Instead of about 85 per cent of salvaged pregnancies, we have now only between 40 and 50 per cent. Therefore it seems to me that the use of corpus luteum extract is practical and valuable in preventing abortion. In the cases in which the fetus is already dead or deformed, the probability is that it does no harm.

ENDOMETRIOSIS

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THIS report comprises a study of the records of 145 private patients on whom a diagnosis of endometriosis was made during a ten-year period from 1930 to 1940. Although the literature on endometriosis is voluminous, comparatively few reports have been compiled based on analysis of a large series of cases. This study was undertaken with the idea that a review of the case histories, comparison of operative procedures and clinical results in a group of patients that could be carefully observed might help to clarify some of the difficult clinical problems associated with endometriosis.

MATERIAL AND INCIDENCE

The 145 patients with diagnosis of endometriosis in this series occurred among 4,763 gynecologic patients, an endometriosis incidence of 3.0 per cent. Of these 145 patients, 80 were operated upon and the diagnosis confirmed by the pathologic findings at operation and the microscopic examination of the tissue removed. The so-called hemorrhagic cysts of the ovary are not included unless associated with evidence of endometriosis elsewhere in the pelvis. All of the 80 proved cases of endometriosis were of the external or pelvic type. Adenomyosis is not included except as one of the associated pathologic lesions. These 80 proved cases of endometriosis occurred among 307 gynecologic laparotomies, an incidence of 26.0 per cent. This figure compares closely with Meigs' 32.2 per cent and Sampson's 21.8 per cent of endometriosis in all abdominal gynecologic operations.

TABLE I. INCIDENCE

Number of patients with diagnosis of endometriosis	145
Number of gynecologic patients	4763
Incidence of endometriosis	3.0%
Number of proved endometriosis cases	80
Number of gynecologic laparotomies	307
Per cent of proved endometriosis cases to all gynecologic laparotomies done	26.0

The statistical data in this paper are compiled only from the 80 proved cases of endometriosis.

AGE INCIDENCE

The youngest patient with endometriosis in this series was 22 years of age and the oldest 62. Table II shows that the greatest incidence

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was between the ages of 34 and 38 years. In this group of cases, 78 per cent occurred between the ages of 30 and 45 years. These figures, I feel sure, do not give a true picture of the incidence of endometriosis in the earlier age groups. Severe types of dysmenorrhea and pelvic pain complained of by patients during the second decade of life may in many instances represent the early stages of this disease. In the third and fourth decades, the symptoms have become more pronounced and the lesions have advanced to a stage where diagnosis is made possible.

TABLE II. AGE INCIDENCE

AGE IN YEARS	NO. CASES	PER CENT
20-23	2	2.5
24-28	5	6.2
29-33	19	23.7
34-38	22	27.5
39-43	15	18.7
44-48	11	13.7
49-53	4	5.0
54-58	1	1.2
59-63	1	1.2
Total	80	100.0

These figures (Table II) of age incidence correspond closely with those of previously reported groups. They only serve to emphasize the tragedy of the frequency of endometriosis in young women.

LOCATION OF ENDOMETRIAL LESIONS

The distribution of the lesions of endometriosis as shown in Table III agrees with other reports in the frequency of involvement of the ovaries. One ovary was the site of 18.2 per cent of the total lesions and both ovaries 17 per cent. Therefore 35.3 per cent of the lesions occurred in the ovaries. The next most frequent site was the cul-de-sac with involvement of the uterosacral ligament area along the posterior aspect of the lower uterine segment. A high percentage of the lesions were in the rectovaginal septum diagnosed by nodules felt in this area on rectal

TABLE III. LOCATION OF ENDOMETRIAL LESIONS

ORGAN	NUMBER	PER CENT OF TOTAL ORGANS INVOLVED (164)
One ovary 30}	58	35.3
Both ovaries 28}		
Pelvic peritoneum	7	4.2
External surface of uterus	4	2.4
Rectovaginal septum	23	14.0
Bladder	2	1.2
Fallopian tubes	2	1.2
Sigmoid	3	1.8
Round ligament	1	0.6
Uterosacral ligament (with adherent rectum)	33	21.2
Uterovesical peritoneum	12	7.1
Vaginal vault behind cervix	4	2.4
Broad ligament	10	6.0
Miscellaneous (utero-vesical orifice, 1; inguinal canal, 1; laparotomy scar, 1; intra-ligamentous endometrial cyst, 1; infundibulopelvic ligament, 1)		

examination. The uterovesical peritoneal fold or anterior cul-de-sac accounted for 7 per cent of the involved areas. One cannot help but be impressed by the same patterns of distribution recurring with striking frequency.

It is not the purpose of this paper to enter into a detailed discussion of the theories of the etiology of endometriosis. Since the first report in 1899 by Russell, of finding of endometrial tissue in the ovary, the work of Cullen, Von Recklinghausen, Lockyer, Novak and others have added to the sum total of our clinical knowledge on this subject. Still the riddle of the etiology of endometriosis remains unsolved. I join with others in paying tribute to Sampson for his outstanding contributions on endometriosis. Sampson's transtubal implantation theory based on careful clinical and laboratory findings is advocated by many gynecologists. However, my clinical observations have converted me to a belief in the theory of lymphatic and vascular metastasis as the mode of dissemination. Sampson himself suggested this possibility in 1922. Halban, Counseller and others have been its strong advocates. It is the only theory that satisfactorily explains the presence of endometrial tissue outside the peritoneal cavity, in the inguinal canal, lymph nodes, umbilicus, and, as has been reported by Schwarz, in the lung. Also the involved areas are so often subperitoneal and in some instances deep seated in the broad ligament and bowel wall. The theory of heteroplasia of celomic epithelium of Iwanoff, Novak and others likewise does not explain these lesions outside the pelvis or why only certain areas of the peritoneum undergo metaplasia. The theory of lymphatic metastasis will explain all the locations in which endometriosis has been described. It also seems to fit in with the clinical picture of islands of endometriosis in close proximity to the uterus in patterns of great similarity as though they followed certain definite channels in their mode of dissemination.

ASSOCIATED PATHOLOGY

In Table IV are listed the pathologic lesions associated with endometriosis in this group of patients. Fibromyomas were the most frequent lesion and were found in 53.7 per cent. Other writers have pointed out the association of fibromyomas and endometriosis. Many theories have been advanced to explain this relationship. Fibromyomas, endometriosis, and adenomyosis frequently are found in the same patient, suggesting that they may have the same etiology. They all develop in women during the menstrual phase of life. Sampson suggested that fibroids may represent the irritative reaction to a proceeding endometriosis. Adenomyosis with endometrial tissue in the center of a myomatous nodule is highly suggestive of such a theory. However, Cullen in his classical studies demonstrated extension of the uterine mucosa into myomatous tissue by direct continuity. Those who believe in the vascular or lymphatic theory of dissemination must admit that

cells from the endometrium would lodge here and there in the musculature of the uterus. Such cells might act as a stimulus to an overgrowth of fibrous and muscle tissue. Certainly external endometriosis wherever found causes a marked cellular reaction in surrounding tissues. We know that fibromyomas rarely occur in smooth muscle elsewhere in the body. On the basis of this theory the uterus is the only smooth muscle organ which might be subject to such a foreign body reaction. Repeated pregnancies might cause changes in the lymphatic channels and with long periods of amenorrhea diminish chances for such cellular metastasis. This might explain the low incidence of fibromyomas in multiparas.

TABLE IV. ASSOCIATED PATHOLOGY

	NUMBER	PER CENT
Myomas	43	53.7
Ovarian pathology		
Simple follicle cysts	20	25.0
Lutein cysts	9	11.2
Fibromas	2	2.5
Hemorrhagic cysts	4	5.0
Pseudomucinous cysts	1	1.2
Papillary cystadenoma	1	1.2
Chronic salpingitis	8	10.0
Endometrial hyperplasia	17	21.2
Adenomyosis of uterus	7	8.7
Sarcoma of uterus	1	1.2
Pelvic abscess (infected cysts)	2	2.5
Pregnancy (intrauterine)	1	1.2
Ureteral stricture and hydronephrosis	8	10.0
Kidney stone	1	1.2
Postoperative adhesions	11	13.7
Uterine retrodisplacement	23	28.7

The high incidence of follicle cysts of the ovary, 25 per cent, and endometrial hyperplasia, 21.2 per cent, might be advanced as an argument in favor of the endocrine theory of endometriosis. A recent study of Brewer and Jones would seem to discredit this theory.

Special attention should be given to the occurrence of ureteral stricture and hydronephrosis in 10 per cent of the cases. The close proximity of the ureter to the involved areas in the broad ligament and uterosacral ligament regions will frequently result in obstructive lesions of the ureters. Such a possibility should be considered in every case of endometriosis. This condition is often overlooked and will account for a residue of pain in many patients operated upon for endometriosis.

Uterine retrodisplacement occurred in 28.7 per cent. Because of its obstructive possibilities, backward displacement of the uterus is considered to be an etiologic factor. Its occurrence in 28.7 per cent of patients in this series is suggestive.

Two of the patients in this report had infected endometrial cysts. Sampson called our attention to this possibility in 1929. Due to the blood content of these cysts and their close proximity to the bowel, it is surprising that this is not a more frequent occurrence.

SYMPTOMATOLOGY

The major symptoms of the patients comprising this study are listed in Table V. This tabulation of symptoms agrees closely with reports of other authors. Certain of these symptoms will be stressed in discussion of the diagnosis of endometriosis.

TABLE V. SYMPTOMATOLOGY

COMPLAINT	NUMBER	PER CENT
Dysmenorrhea	53	66.2
Menorrhagia	25	31.2
Metrorrhagia	8	10.0
Polymenorrhea	7	8.7
Uterine bleeding (brownish discharge pre- and postmenstrual)	12	15.0
Elevation temperature leucocytosis	7	8.7
Lower abdominal pain	34	42.5
Pain inguinal region	3	3.7
Pain in thighs	8	10.0
Sacral back pains	23	28.7
Rectal pains	6	7.5
Bladder symptoms	12	15.0
Gastrointestinal symptoms	15	18.7
Upper abdominal reflex pains	5	6.1
Dyspareunia	6	7.5
Amenorrhea	6	7.5
Headache	7	8.7
Sensation of pressure in pelvis	16	20.0
Nervousness	17	21.2
Constipation and obstipation	24	30.0
Pain referred to area of kidneys	9	11.2

TABLE VI. TYPE OF DYSMENORRHEA

Pre- and intramenstrual pain	25.0
Dysmenorrhea all of menstrual life	21.1
Acquired dysmenorrhea	11.2
Premenstrual pain	15.0
Postmenstrual pain	8.7
Normal periods	18.6

TABLE VII. STERILITY

	NUMBER	NUMBER CHILDREN	STERILITY PER CENT
Single	17	0	
Married	63	29	46

The occurrence of barren marriages is recognized to approximate 12 per cent. Patients with endometriosis in this group were almost four times as sterile as the average female patient.

TABLE VIII. PREVIOUS OPERATIONS

TOTAL NUMBER OF PATIENTS	PATIENTS WITH PREVIOUS ABDOMINAL OPERATIONS	PER CENT	DILATATION AND CURETTAGE	PER CENT
80	14	17.5	5	6.2

PREOPERATIVE DIAGNOSIS

A correct preoperative diagnosis was made in 48.7 per cent of the reported cases. Among the 41 patients on whom an incorrect diagnosis was made, 26 had large fibromyomas which overshadowed the usual diagnostic findings of endometriosis (Table IX).

TABLE IX. PREOPERATIVE DIAGNOSIS (80 PATIENTS)

	NUMBER	PER CENT
Correctly diagnosed	39	48.7
Not correctly diagnosed	41	51.2

The diagnosis of endometriosis is not always easily made. Extensive lesions may exist without any subjective symptoms. Twenty per cent of my patients had menses free of pain and were normal in other respects. In no other gynecologic condition is a carefully taken history so important as an aid to correct diagnosis. The following symptoms if present in the history are of diagnostic value: (1) *Dysmenorrhea* of an acquired type, or an accentuation of pre-existing dysmenorrhea; (2) *premenstrual pain*, lower abdominal discomfort resembling menstrual cramps often of a crescendo type beginning a few days or a week or more before the onset of menstruation; (3) *abnormal uterine bleeding* in the form of menorrhagia or metrorrhagia or frequently intermenstrual brownish-colored uterine discharge; (4) *pain* in one or both lower abdominal quadrants or suprapubic areas which may be constant in character, although often its periodicity is significant (a sense of pelvic pressure described as a bearing down sensation as if everything were falling out of the pelvis); (5) *pain* referred to the groin, hip, or thighs; (6) *dyspareunia*, acquired and unexplained by other findings; (7) *obstipation* and *constipation*, often related to the time of menstruation (rectal discomfort described as a sensation that would be relieved by bowel evacuation); (8) *sterility*, unexplained after a careful sterility study; (9) *sacral backache*, menstrual type of headache, reflex gastrointestinal symptoms and bladder symptoms.

The physical findings on vaginal examination are additional aids in diagnosis. The presence of enlarged, adherent ovaries without evidence of pre-existing pelvic infection is strongly suggestive of endometrial cysts. The character of the posterior vaginal vault is of great significance. One gets the impression of a shallow posterior vaginal fornix. There is a sense of resistance and thickening of the tissue in this area. At times nodules are palpable posterior to the cervix. These nodules are more readily palpable on rectal examination with additional evidence of induration in the area of the uterosacral ligaments. Movements of the uterus are restricted. If a retrodisplacement is present, although not adherent, effort to bring the fundus forward is more difficult than in uncomplicated retroversions. Often a distinct lack of mobility of the

entire uterus is noted. This is particularly noticeable in lifting the cervix and fundus upward and forward toward the anterior abdominal wall. This fixation of the lower uterine segment accounts for the increased difficulty in mobilization of the uterus when doing a hysterectomy associated with endometriosis. There is additional evidence of unusual pelvic tenderness on vaginal examination.

TREATMENT

The treatment of endometriosis will depend on the type of symptoms, the age of the patients, the extent of the lesions, and associated pelvic pathology. It is well known that removal of all ovarian tissue will cause regressive changes in endometriomas. This may be accomplished either by bilateral oophorectomy or by irradiation. However, the frequency of endometriosis in young women presents a problem in treatment which calls for mature surgical judgment.

The treatment of endometriosis in this group of patients was mainly one of conservatism. Eighty patients were operated upon out of the 145 patients with diagnosis of endometriosis. Of these, 53 per cent had associated fibromyomas of the uterus which made surgical interference necessary. The decision for operation was based on the severity of the symptoms. Patients having endometriosis deserve a frank discussion of their condition with explanation of the cause of their premenstrual discomfort and other pelvic symptoms. Intelligent patients will endure their discomfort unless severe and prefer a status of periodic observation rather than the necessity of a mutilating pelvic operation. Observations on patients operated upon during the fourth and fifth decades of life for fibromyomas with associated endometriosis convinces me that this condition is not always a progressive pathologic lesion; that many small areas of endometriosis cause few if any symptoms and that other extensive growths have remained quiescent as a result of adhesions and inflammatory reaction about them.

There is a malignant type of endometriosis which is invasive and destructive accompanied by severe symptoms which will warrant radical treatment. In some instances extensive involvement of both ovaries makes conservation of ovarian tissue impossible.

Table X gives the types of surgical treatment in this group of patients.

The guiding principle in treatment has been relief of symptoms by removal of major lesions and if possible preservation of ovarian function. Such treatment was carried out in 80 per cent of the entire group. All of the patients in the 20 to 30 age group were treated conservatively. In 6 of the 8 patients in this age group, ovarian and reproduction functions were conserved. Necessity for reoperation or irradiation is preferable to initial radical surgery in young women. Radical surgery was carried out in 8.7 per cent of the 30- to 40-year age

TABLE X. TYPE OF SURGICAL TREATMENT (80 PATIENTS)

	AGE			
	20-30	30-40	40-50	50-62
Number of patients	8	45	21	6
Radical	0	7	5	4
Hysterectomy with conserva- tion of one ovary	2	18	16	2
Conservative	6	20	0	0

group and 11.2 per cent in the 40- to 60-year age group. Hysterectomy with conservation of one ovary, 47.5 per cent of the patients, was the most frequent type of operation. It is generally accepted that following hysterectomy ovarian function gradually diminishes. This may account for the fact that in my patients endometriomas not entirely removed with this type of operation cause few if any postoperative symptoms. No attempt was made to remove areas of endometriosis involving the rectum or rectovaginal septum. Surgical removal of such areas is dangerous. Extensive involvement of the rectovaginal septum causing symptoms is best treated by bilateral oophorectomy. Irradiation was not used as the initial method of treatment in any of my patients. Surgery is preferred, because it gives the opportunity for conservatism with removal of large endometriomas and the correction of associated pelvic pathology.

RESULTS OF TREATMENT

There was no mortality in this series of 80 patients operated upon for endometriosis. Follow-up study was possible in 73 of the 80 patients. A conscientious effort was made to evaluate the results of treatment which are listed in Table XI. Patients following operation for endometriosis will have a greater morbidity than those following clean-cut pelvic operations due to the additional trauma and raw areas incident to the enucleation of large endometriomas. Although the relief of major symptoms in the radically treated group are excellent, one cannot help but be depressed over the high incidence of vasomotor and nervous symptoms in these castrated women. In the group with preservation of ovarian or reproductive function, only 29.1 per cent were relieved of their major symptoms. Additional irradiation treatment for relief of symptoms was necessary in 12.6 per cent of these patients. Doubtless others in this group will in time require further treatment. However, 12.6 per cent of the patients treated conservatively became pregnant, with delivery of normal babies. Two of these patients were barren eleven and twelve years, respectively, prior to operation. The number of patients is too small to draw definite conclusions as to the value of surgery in the correction of sterility associated with endometriosis. It would seem that excision of major ovarian lesions, correction of tubal adhesions, and associated retrodisplacements may increase the chances

TABLE XI. RESULTS OF TREATMENT (73 PATIENTS)

	CONSERVATIVE UTERUS AND ONE OR BOTH OVARIES CON- SERVED	CONSERVATIVE HYSTERECTOMY ONE OVARY CONSERVED	RADICAL HYSTERECTOMY BILATERAL OOPHORECTOMY
Number of patients with adequate follow up	24	35	14
Relief of chief complaints	29.1%	71.4%	85.7%
Partial relief	54.1%	25.7%	7.1%
No relief	16.6%	2.8%	7.1%
Extreme nervous symptoms	0.0%	11.4%	64.2%
Pregnancies	12.6%	0.0%	0.0%
Subsequent treatment			
Irradiation	12.6%	0.0%	0.0%
Surgery	0.0%	0.0%	0.0%

for conception in some patients. Hysterectomy with preservation of some ovarian tissue seemed to give the best end results in this series of patients.

SUMMARY

1. Eighty patients with proved endometriosis occurred in 307 gynecologic laparotomies, an incidence of 26 per cent.

2. Endometriosis is a disease of middle menstrual life with an incidence of 78 per cent between the ages of 30 and 45 years in the reported group of cases.

3. The majority of the endometrial lesions occurred in the ovaries, anterior and posterior cul-de-sac, and the rectovaginal septum.

4. The frequent occurrence of external endometriosis, adenomyosis, and fibromyomas in the same patient suggests that these may have the same etiology. Belief in the theory of vascular and lymphatic metastasis as the mode of dissemination of endometriosis is expressed.

5. Dysmenorrhea, abnormal uterine bleeding, lower abdominal pain, sacral backache, and dyspareunia are the most frequent symptoms of endometriosis.

6. Conservatism in the treatment of endometriosis is justified by the end results in the cases reported.

7. Endometriosis with its riddle of etiology, its devastating effects on the reproductive organs of young women, its unknown factors of prevention remains a real challenge to every gynecologist for the solution of these problems.

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DISCUSSION

DR. A. D. CAMPBELL, MONTREAL, CANADA.—The incidence of endometriosis in the experience of most of us is that observed by Dr. Holmes. These figures are conservative and represent only those cases with more or less active endometriosis. In many instances the condition may exist in subclinical form and be labeled as post-operative adhesions.

Often, upon opening the abdominal cavity, one encounters scar tissue at the junction of the broad ligament with the uterus or along the uterosacral ligaments or as dense adhesions fixing the lower part of the sigmoid to the peritoneal surface of the vaginal vault. Certain as one may be that the etiology of such scars is a sequel to endometriosis, one cannot prove this point in the absence of histologic evidence. If nonactive or healed endometriosis were added to active endometriosis, the incidence of this condition would mount considerably.

At this point may I suggest that the term "dysmenorrhea" be less promiscuously used than at present. In 1926 Sir Henry Beekwith Whitehouse suggested restricting the term "dysmenorrhea" to embrace a certain symptom complex and that pain associated with menstruation be termed "menorrhagia." I subscribe to this differentiation.

No one theory of etiology of endometriosis is applicable to all cases. In endometriosis of the vulva and the umbilicus one does not need, however, to seek special theories when one can demonstrate a patency in the canal of Nuck or a scarred hernial tract extending from the abdominal cavity into the umbilicus. In this connection I have had the opportunity to dissect carefully the umbilical area in cases of ectopic gestation presenting so-called Cullen's sign. I have carried out similar dissections on endometriosis of the umbilicus and found scar tissue which undoubtedly was the remains of the small hernial canal through which transplants escaped from the abdominal cavity.

The treatment of every case must be judged in the light of its particular circumstances. Were it not for the fact that the life history of endometriosis is problematical and that the process becomes so arrested that in rare cases pregnancy has followed, one would have grounds for the most radical treatment in all cases of endometriosis. In general, however, in no case where endometriosis has spontaneously developed will a patient become pregnant so long as endometriosis remains active.

When marked endometriosis involves the rectovaginal septum, I feel that panhysterectomy with complete resections of the ovaries is wise, for here, probably more than in any other location, is malignancy likely to be superimposed upon this lesion. In either the conservative or radical surgical treatment of endometriosis one must at operation completely peritonize all raw areas. Where the pelvic peritoneum is destroyed, I strongly suggest peritonization by a form of marsupialization

of this area. The patient is then left with a completely peritonized pelvic basin. Where one is more conservative, in addition to this precaution, it has been my practice for years to perform a presacral sympathectomy. By so doing one may with confidence be less radical and leave the patient with at least some ovarian tissue. One, too, can reassure the patient that she will in all probability be free from pain.

Endometriosis will not be completely understood, either from the standpoint of etiology, of its life history, or its sequelae, until we understand more clearly the relationship between ovarian function and that of the endometrium. I am firmly convinced that endometriosis is primarily an endocrinologic problem. Experience has clearly demonstrated to me that in certain instances sterility, endometriosis, and ectopic gestation are due to the same endocrinologic influences.

DR. JOE V. MEIGS, BOSTON, MASS.—In May, 1941, I reported that in my private practice of 400 patients with gynecologic conditions necessitating abdominal surgery, 28 per cent had endometriosis; 112 out of 400. In the same period of time at the Massachusetts General Hospital, of 400 patients necessitating abdominal surgery only 5.8 per cent had endometriosis. In private practice there is, therefore, much more endometriosis than in a charity hospital practice.

Endometriosis is not a true tumor but a physiologic response to an abnormally uninterrupted menstrual career. Patients should not menstruate as often as they do without an intervening pregnancy. I think that because of the economic trends of the times we are allowing women of the private patient class to go too long without a pregnancy. That is the whole crux of the endometriosis situation. Stimulation by something (estrin) is causing the celomic epithelium to grow.

I believe we must change our ideas and instead of leaving an inheritance to our daughters when they reach about 50 years of age, we should encourage them to marry when young, at 18 or 21, and help them financially then instead of waiting until they are older.

I believe that delayed pregnancies are responsible for this entity. If endometriosis commences, fertility is immediately lowered. In my private practice, the fertility of patients with endometriosis was 65 per cent as against 90 per cent in those that did not have endometriosis. Fifty per cent of the patients I have operated upon since June have had endometriosis. There must be something wrong somewhere.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—In the clinical diagnosis I find a rather valuable guide in the development of a new type of dysmenorrhea superimposed upon the previously existing type. If we study these cases carefully, this dysmenorrhea is found to be of the peritoneal type. By recognizing this symptom the percentage of accurate diagnosis is increased.

As to treatment, the young individual in whom reproduction is essential must be relieved of a very real pain. For that I have found very useful the operation of presacral sympathectomy, combined with bilateral ovarian neurotomy. In our group of cases so treated, a perfectly normal menstrual cycle has been resumed after the initial menorrhagia of from one to three cycles. I have done this operation on 5 individuals of whom 3 have since become pregnant. One patient with a peri-ureteral infiltration was not affected by the presacral sympathectomy, and was elsewhere given a subcastration x-ray treatment. She became pregnant and aborted, the fetus having a central nervous defect.

I am in thorough accord with Dr. Meigs' remarks. There is something in the mode of life in the so-called higher classes which accounts definitely for 80 per cent of their functional disturbances. Ninety per cent of the psychoneuroses come from the same source which is reflected in gynecologic symptomatology.

DR. JAMES R. GOODALL, MONTREAL, CANADA.—Endometriosis is a general pelvic disease operating from a general pelvic cause, and it is a mistake to separate

endometriosis into various subdivisions. All forms of endometriosis arise from the endometrium, but it is very important to find out from what part of the endometrium the endometriosis has taken its origin. It is known, of course, that when the endometrium responds to the menstrual cycle only the surface layers are affected. If endometriosis has arisen from cells desquamated from the surface of the endometrium, by the "spill" method, we invariably get chocolate cysts because these cells respond to the hormones of the menstrual cycle. On the other hand, if the endometriosis starts from the basal layer of the endometrium, it does not respond to the cycle of menstruation as it penetrates the uterine wall.

The methods of extension of endometriosis are in every way analogous to the methods of spread of infection. In my textbook on *Puerperal Infections* I stated that the extension of the disease was by one of four methods: First, that the extension was local; second, that it extends by the blood vessels; third, by the lymphatics; and fourth, by surface continuity out of the tubes, and so it is with endometriosis.

If we examine all of the organs of the pelvis in endometriosis, we find various correlated lesions which otherwise would not have been recognized except by biopsy. One example is the hypertrophy of the uterine musculature which is a response to the menstrual cycles. We have, however, also found a new disease which is correlated with endometriosis, although sometimes found independently, and that is peritoneal sclerosis. Oftentimes when opening the abdomen I have diagnosed endometriosis, when I had not suspected it, by the thickness of the peritoneum, in some cases so thick that when the scissors go through the vesicouterine fold it gives a sound like cutting through cartilage.

There is but one common cause of endometriosis. I am more convinced than ever that endometriosis is an expression of hyperestrinism. I do not think this will ever be demonstrated conclusively, because hyperestrinism may be of two types, an absolute hyperestrinism or a relative one. If I give a patient a very large dose of estrogen and examine the urine in the next twenty-four to forty-eight hours, I may recover very little of it, but if I follow with a dose of progesterone, an increase in estrin excretion is noticeable almost immediately. That proves, I think, that there is a chemical combination between estrin and the endometrial cells although an examination of the blood or urine would not show any degree of hyperestrinism.

I was delighted to hear Dr. Meigs' remarks about sterility. In my recently finished book on *Endometriosis* I advocated exactly what Dr. Meigs has advocated today. Not only should our young girls marry earlier but they should have several children. The nulliparous married woman is just as susceptible to endometriosis, however, as the unmarried young girl.

I have had an eye opener in the last year. We have been studying the relation of the ovary to pregnancy and have found that the ovary ceases to function at about the sixth month of pregnancy. From that time on it resembles very much the ovary of a senile woman. We have traced that through the later months of pregnancy and through the puerperium. If you remove the ovaries of a woman immediately after her first menstruation following pregnancy it will show the most astounding picture. The ovary ripens anywhere from 4 to 12 ova all at once to bring about that menstruation and the regeneration of all the pelvic organs, notably the uterine musculature. This supplements what Dr. Meigs has said. I think that there we are touching on something which is absolutely vital and that endometriosis is the result of our so-called civilization.

MANAGEMENT AND OUTCOME OF LABOR IN 742 WOMEN WITH BORDERLINE PELVES*

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THE study of this particular group of women classified as having borderline pelves, was begun July 30, 1936, and terminated Aug. 1, 1941, a period of five years. All of them were indigent and received prenatal care from the Health Department of the District of Columbia. Their relative frequency may be stated as one-twelfth of the entire clinic attendance during the five-year period.

Probably the most important mechanical factor in obstetrics is the pelvis. Where a large number of patients and many clinicians are involved, it is necessary to adopt certain standards of recognition for borderline and contracted pelves. For further observation and x-ray study, patients in such category may then be referred to the "abnormal" clinic, which is conducted by a single individual.

It is essential to recognize pelvic contraction, and for that reason we had established a broad standard of selection, which would include almost any case of potential danger. Thus all primiparas with a diagonal conjugate diameter of 11.5 cm. or less, and all multiparas with a diagonal conjugate of 11 cm. or less, regardless of previous history of childbirth, have been referred to the x-ray clinic.

The diagonal conjugate was measured on the Douglas pelvimeter. In the 760 cases that ranged from 8.5 to 11.5 cm., the actual length of each diagonal conjugate, the frequency, and color incidence are shown in Table I.

My technique of lateral pelvic roentgenography in which film scales are used to measure films¹ was selected for the study of these patients, because of its inexpensiveness, simplicity, and accuracy. By this procedure the degree of engagement of the fetal skull is readily noted, and disproportion when present may be recognized. All the important landmarks of the pelvis are readily identified, and the true conjugate diameter, extending from the middle of the upper border of the symphysis to the sacral promontory, is unmistakable.

What the author refers to as the *available true conjugate diameter* extends from the posterior surface of the symphysis to the sacral

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

TABLE I

D.C.	TOTAL	WHITE	COLORED
8.5	2		2
8.8	1		1
9.0	3		3
9.5	6	1	5
9.8	1		1
10.0	29	4	25
10.3	8	1	7
10.5	57	4	53
10.8	30	1	29
11.0	345	40	305
11.1	1		1
11.3	25	3	22
11.4	1		1
11.5	251	28	223
Total	760	82	678

promontory; this is about 7 mm. less than the true conjugate. In this study, all references are made to the true conjugate, since that is the custom of most authors.

DIAGONAL VERSUS TRUE CONJUGATE

In a previous study,² it was shown that Smellie's rule of subtracting 1.5 to 2 cm. from the diagonal to obtain the true conjugate applied in 8 per cent of cases; and in 89.5 per cent the difference between these two diameters was less than 1.5 cm. I also mentioned the existence of pelves in which the length of the true conjugate approaches and even exceeds that of the diagonal; and in the present study I have found several such. If the true conjugate were not measured with precision, but merely estimated by Smellie's rule, some of the patients with ample inlets would probably have been subjected to cesarean section.

At present I am reporting on 760 borderline pelves in which a comparison between the diagonal and true conjugates could be made. Of these women 678 were colored and 82 were white; 497 were primiparas and 263 were multiparas.

The true conjugate diameters, not estimated, but actually measured, varied from 7 cm. to 14.5 cm. *There is no constant relationship between the diagonal and true conjugates.* The most common true conjugate in 760 cases was 10 cm.; this was found 68 times.

For any particular diagonal conjugate, there may be a wide variation of true conjugates. Reference is made to a few examples:

In two cases where the diagonal conjugate measured 8.5 cm., the true conjugate was 7 cm. in one and 10.4 cm. in the other. One of course required cesarean section and the other did not.

In 30 cases, a diagonal conjugate of 10.8 designated a true conjugate varying between 8.4 and 11.5.

There were 25 patients with a diagonal conjugate of 11.3. Here the true conjugates varied between 9.2 and 12 cm.

Of the 760 cases, the diagonal conjugate exceeded the length of the true conjugate in 443. The two diameters were equal in 56 women; and in 261, the diagonal conjugate was smaller than the true conjugate.

For a long time, I have directed attention to the variable relationship between these two important diameters. My original observations were made with the "obstetric inelinometer"²³ and the findings have been repeatedly confirmed in my roentgen pelvimetry studies. Variability in size, of what I have called *the obstetric angle*, accounts for the varied relationship in different women. By the obstetric angle is meant the angle between the symphysis and diagonal conjugate diameter. It is readily seen that a wide angle will include a large true conjugate, and an acute angle will subtend a short one. By the use of pelvic roentgenography, this information is readily obtained, without mathematical calculation.

It was noted also, that

1. Seventy-nine cases, or 10.4 per cent, conformed to Smellie's Rule.
2. In 16 women, or about 2.1 per cent, the true conjugate was more than 2 cm. less than the diagonal. In this group of course the prognosis is least favorable, depending upon the length of the diagonal conjugate diameter.
3. There was a group of 665 women, or 87.5 per cent, in which the length of the true conjugate varied between 1.4 cm. less to 3.4 cm. more than the diagonal. Naturally, patients falling into this large group are benefited by a more favorable prognosis.

These observations check to a remarkable degree with the findings in the small series of 80 cases already referred to, in which the proportions were, respectively, 8 per cent, 2.5 per cent, and 89.5 per cent.

Unfortunately, statements by authorities, relative to the management and outcome of labor in borderline pelves, have not been based upon accurately determined true conjugates, but upon those estimated with the use of Smellie's Rule.

One may realize the false concepts that might have been arrived at in the present series of cases had they been managed by merely measuring the diagonal conjugate and applying Smellie's Rule, instead of using x-ray to measure the true conjugate. Suffice it to say, that treatment would have been much more radical, not individualized, and the results less favorable than this study will show.

The work here presented has been particularly interesting to me because of the manner in which it was conducted. I have had an opportunity to examine all of the patients; I have taken an active part in the roentgenography of each of them, interpreted the films, read the measurements, predicted the prognosis and advised treatment. All were followed from the prenatal clinic through delivery.

COMPARISON OF PROGNOSIS AND OUTCOME

This was possible in 742 cases out of the 760, since 18 had not delivered.

Prognosis was based upon interpretation of film; in multiparas some consideration was given to previous childbearing.

In my opinion, when prediction of prognosis is greatly influenced by roentgenographie findings, as is my custom, the effect of color is not as important as had been heretofore considered. For we are able not only to measure the head and pelvis, but also to note cephalopelvic relationship.

Of course, where one does not employ this procedure, his judgment must be influenced by all other less dependable facts and theories.

Prognosis was stated as follows:

1. Favorable
2. Guarded
3. Test labor
4. Probable cesarean section

In every case the predicted prognosis and suggested method of treatment were recorded and sent to the person or hospital responsible for delivery, before the onset of labor.

Table II represents clearly the comparison between prognosis and type of delivery or outcome in this particular series. Although it should not be followed as a guide, it shows that lateral pelvimetric study may have a conservative effect upon the conduct of the obstetrician, as well as enable him to predict prognosis with some degree of precision.

TABLE II. PROGNOSIS

Prognosis was predicted as favorable, guarded, test labor, and cesarean section. Under each of these four headings is found the number so predicted. Reading across the page gives the number of each type of delivery in each of the four groups.

		TOTAL	FAVOR- ABLE	GUARDED	TEST LABOR	CESAR- EAN SECTION
Total		742	494	82	144	22
Outcome	Normal	580	413	54	108	5
	Forceps	99	64	13	20	2
	Cesarean section	46	8	11	13	14
	Breech extraction	12	6	3	3	-
	Version and extraction	4	2	1	-	1
Craniotomy		1	1	-	-	-

1. A favorable outcome was predicted in 494 women. What actually happened in these cases was as follows: 413 delivered normally; 64 were forceps deliveries, mostly prophylactic; 6 breech extractions; 2 version and extraction; 1 craniotomy on a dead hydrocephalic baby; and 8 cesarean sections which will be accounted for under the heading "Analysis of Cesarean Sections."

2. The prognosis was considered guarded in 82 cases. Fifty-four of these delivered normally; 13 were delivered with forceps, 3 by breech extraction, 1 by version and extraction, and 11 by cesarean section.

3. Test labor was advised in 144 women. One hundred and eight of these delivered normally, 20 were delivered with forceps, 3 by breech extraction, and 13 by cesarean section.

4. Probable cesarean section was the prognosis predicted in 22 women. Only 14, however, were so delivered.

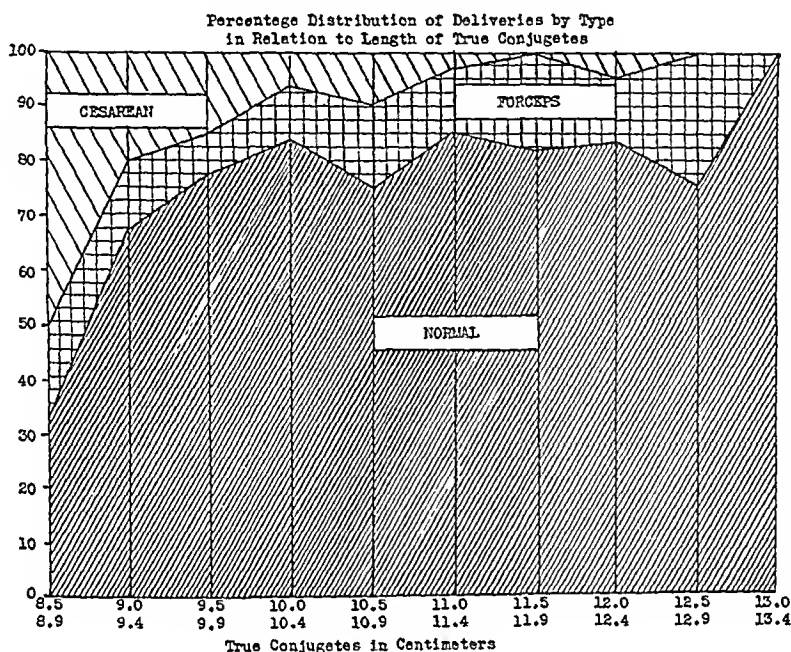


Fig. 1.—Diagonal conjugates below 8.5 cm. are not represented in this graph because the exceedingly small number of cases would probably create a false impression. Likewise diagonal conjugates of 13.5 cm. and over are omitted because under ordinary circumstances all cases in this category should deliver normally.

Breech, version, and extraction and craniotomy are omitted because the relatively few cases in these groups would merely confuse the graph.

The expectation for normal delivery improves as the size of the true conjugate increases. Of course cesarean sections done for reasons other than pelvic contraction, as well as prophylactic forceps, do interfere somewhat with the above expectancy.

TYPE OF DELIVERY

According to type of delivery, the 742 borderline cases were distributed as follows:

Normal	580, or 78.2 per cent
Forceps (including prophylactic)	99, or 13.4 per cent
Cesarean section	46, or 6.2 per cent
Version and extraction	4, or 0.5 per cent
Breech extraction	12, or 1.6 per cent
Craniotomy	1, or 0.1 per cent

ANALYSIS OF CESAREAN SECTIONS IN THE FOUR GROUPS

1. *Favorable*.—In this group of 494 women, there were 8 cesarean sections; an incidence of 1.6 per cent. One operation was done because

of a large fibroid; 2 because of previous cesarean section; 1 for placenta previa; 1 was twins, probably not diagnosed; and in the other 3, there was no engagement after long labor.

2. *Guarded*.—Out of 82 cases, there were 11 cesarean sections, an incidence of 13.4 per cent. Four of the operations were done because of breech presentation in marked borderline pelvis.

3. *Test Labor*.—In 144 cases there were 13 cesarean sections, an incidence of 9 per cent.

Two were done because of previous cesarean section; 1 because of previous difficult labor; 1 for breech presentation in a primipara; and 1 for impacted transverse presentation. There were 5 sections done without adequate test labor. The remaining 3 did have adequate test labor.

4. *Probable Cesarean Section*.—Out of 22 such patients, only 14 were sectioned; an incidence of 63.6 per cent. Of the other 8, 5 delivered normally (of which 1 was premature), 2 were delivered with forceps, and 1 by version and extraction. This group shows the greatest discrepancy between prognosis and outcome; such error tends toward conservatism.

If an occasional patient had not delivered prematurely, and if some had not been sent for x-ray too early in pregnancy, the prediction of prognosis, particularly in this group, might have been more accurate.

TYPE OF DELIVERY THAT OCCURRED IN PELTS OF ACCURATELY DETERMINED TRUE CONJUGATES OF VARIOUS LENGTHS

It will be noticed that the incidence of each type of delivery is quoted for every half centimeter variation in the length of the true conjugate diameter. The percentage frequency is shown in the graph, while numerical frequency is stated in Table IV.

TABLE IV

	NORMAL	FORCEPS	CESAR- EAN SECTION	BREECH	VERSION AND EXTRAC- TION	CRANIOT- OMY
7.0- 7.4	-	-	1	-	-	-
7.5- 7.9	1	-	1	-	-	-
8.0- 8.4	2	1	1	-	-	-
8.5- 8.9	2	1	3	-	-	-
9.0- 9.4	27	5	8	-	-	-
9.5- 9.9	56	6	10	1	1	-
10.0-10.4	122	16	7	3	-	-
10.5-10.9	90	20	10	3	1	-
11.0-11.4	122	16	3	1	2	-
11.5-11.9	88	19	-	3	-	-
12.0-12.4	42	6	2	1	-	1
12.5-12.9	18	6	-	-	-	-
13.0-13.4	7	-	-	-	-	-
13.5-13.9	2	2	-	-	-	-
14.0-14.4	1	-	-	-	-	-
14.5-14.9	-	1	-	-	-	-

Similarly, the type of delivery according to length of diagonal conjugate is known but not stated, because the diagonal conjugate is a false index for prognostication. One cannot surmise the length of the true conjugate from the diagonal.

MATERNAL MORTALITY AND STILLBIRTHS

There was one maternal death. This patient died twenty-six days after a normal delivery. She was an old rheumatic and cause of death was acute bacterial endocarditis.

There were only 9 stillbirths. Four were macerated and the mothers had syphilis. The mother of one had pneumonia. The mother of another had pre-eclamptic toxemia. One was an impacted transverse presentation. One had a craniotomy. In one the cause of death was not determined.

SUMMARY

In the prenatal clinics of the Health Department of the District of Columbia the incidence of borderline pelvis was one-twelfth of the entire registration, over a five-year period.

The results of roentgen measurements indicate that Smellie's Rule should be discarded.

The lateral pelvic roentgenogram was the most important factor, governing treatment in these women; 78.2 per cent of them delivered normally; 13.4 per cent were delivered with forceps. Cesarean section was performed in 6.2 per cent; some sections were done for causes other than pelvic contraction.

Of the 742 cases, a favorable outcome (meaning by favorable outcome a normal delivery or average forceps) was predicted in 494. Almost 477 were so delivered, since there were some difficult forceps deliveries.

The degree of correct prognostication and the moral support obtained from the lateral roentgenogram have been very gratifying to the author, and have been of definite assistance to those performing the deliveries.

Grouping pelvis according to true conjugates that are obtained by Smellie's Rule, and thus directing treatment, which is the conventional method, is unscientific and misleading.

CONCLUSIONS

1. It is significant that no reference has been made to modern pelvic classifications denoting types. Likewise, reference to anteroposterior roentgenography has been avoided.

From the point of view of management, mere classification of pelvis is of less value than the lateral pelvimetric roentgenogram except where marked distortion or where some very unusual departure from normal structure exists.

As regards the anteroposterior roentgenogram, it is of definitely less value than the lateral. It is of aid in measuring transverse contraction of the inlet, but such contractions that are marked enough to prevent engagement are extremely rare. None was encountered in this series.

2. For practical purposes the author regards pelvis as normal, borderline, or absolutely contracted.

What to do with the normal and definitely contracted ones is generally known.

3. Borderline cases may be detected by referring every primipara with a diagonal conjugate of 11.5 cm. or less and every multipara with a diagonal conjugate of 11 cm. or less, for a lateral pelvic roentgenogram, preferably late in pregnancy.

Mensuration and interpretation of the film will establish sound basis for forming an opinion; this is an intelligent method of approach.

It not only will help to decide whether to give a patient a test of labor, but in correlation with the character of the labor, will afford some idea as to how much of a test is warranted.

Cooperation is gratefully acknowledged to the Staff of Dr. George C. Ruhland, Health Officer, for the analyses involved in this study.

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WASHINGTON MEDICAL BUILDING

DISCUSSION

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—Dr. Jacobs follows the rule of most authors in designating the anatomic conjugate of the inlet as the true conjugate, although he recognizes and emphasizes the importance of the obstetric conjugate or what he calls the "available" true conjugate. There is some disparity of practice in relation to these terms. One of the most important uses of lateral pelvic roentgenography is the ability which it gives us to determine accurately the obstetric or available conjugate. Inasmuch as either end of this diameter is a variable, we have in the lateral x-ray for the first time the means of its accurate determination. In our own clinic, it is this conjugate which we endeavor to estimate as a basis for prognosis and think of it as the true conjugate.

I concur with Dr. Jacobs in the invalidity of Smellie's formula. We have noted in our own work, however, a very much closer correspondence between the clinically observed length of the diagonal conjugate, and the roentgenographic estimation of the available conjugate, than has heretofore been recognized in ordinary pelvimetric practice. In the majority of cases the difference does not exceed half a centimeter.

I also agree with Dr. Jacobs that if one were compelled to depend on one x-ray film, the transverse plate would be the most useful. I do not agree with him, however, that a wholly competent roentgenographic study of the pelvis can be made with such films. In our own practice we include such films in our pelvic roentgenographs, but use instead of Dr. Jacobs' screens, a modification of the Weitzner rule which our own x-ray laboratory has devised. This has the advantage of permanently including in every film a means of direct measurement.

We also use stereoroentgenographs of the pelvic inlet and of the outlet, for it does not seem to us that prognosis can be entirely predicated upon the length of the AP diameter and the inclination of the pelvis, on which Dr. Jacobs appears to depend. The configuration of the inlet is to us important. It seems self-evident that between any two pelvis with the same true conjugate, the prognosis might vary considerably if one presented a typical android inlet, the other a typical anthropoid

inlet. Moreover, we wish to include in our prognosis not only the question of engagement and descent of the head through the inlet, but also potential difficulties in the midplane and at the outlet. We feel that in order to do this properly, films in two other planes must be correlated to those taken in the transverse aspect of the pelvis.

The real accuracy of prognosis is particularly hard to estimate. For instance, in Dr. Jacobs' first group of 494 women, 477 delivered "favorably," that is, either spontaneously or by "ordinary" forceps. One might wonder what is embraced in the term "ordinary" forceps, and exactly what the indications and conditions were in those cases so delivered but not included in the number which were "mostly prophylactic." For completion of the whole statistical picture, it would be interesting also to know what happened to the more than 90 per cent of Dr. Jacobs' total material which was not subjected at all to this careful type of x-ray prognosis. They should all, of course, have been expected to deliver "favorably."

I find that in 1,000 consecutive cases selected at random of full-term deliveries on our service, the vast majority of the patients had not been subjected to critical estimation and prognosis, 93.6 per cent delivered either spontaneously or by forceps, as compared to 96.5 per cent of the group in Dr. Jacobs' series who had been most carefully determined as presenting wholly favorable prognosis.

The difficulty of estimation to accuracy of prognosis becomes greater in relation to the equivocal groups of Dr. Jacobs' classification. In the second group the prognosis was considered guarded. This might be paraphrased by saying that possible trouble was expected in them. Was the prognosis accurate in the 54 of the 82 which escaped this possible trouble or in the 28 who actually encountered trouble? In his third group in which "test labor" was advised, the prognosis might be stated in other terms to represent the probability of trouble. Again, was the prognosis accurate in the 108 who escaped trouble or in the 36 who actually ran into trouble? I do not want to belabor this question. It is, after all, not especially important; yet as nearly as I am able to compute it, Dr. Jacobs has been accurate in 88 per cent of the prognoses of all his cases. In our own work we are not able to credit ourselves with accuracy of prognosis in much over 80 per cent. However, the percentage of accuracy is not a measure of the value of this work. The provision of data and the furnishing of warning signals to the men responsible for the eventual conduct of the labor in these cases is all that we may hope to accomplish. In the last analysis, management must depend on the judgment of the individual under whose observation the actual labor performance takes place.

DR. WILLIAM T. McCONNELL, LOUISVILLE, KY.—A great many babies are lost because of our inability to determine accurately the relative proportion between a given baby and a given pelvis at a given time. In practically every paper on cephalopelvic disproportion emphasis is laid on the estimation of pelvic diameters and types of pelves. But I have yet to hear or read a paper setting forth any practical method of determining the relation between the size of a given head and the pelvic capacity of the mother at the time of delivery.

We must bring this thought into our work and into our teaching. It is not a question of how big the pelvis or the baby may be, but of how that baby's head matches up with that pelvic capacity at that particular time. The average roentgenologist is of very little help, for his report usually reads something like: "Baby apparently at full term; apparently no cephalopelvic disproportion." Men doing obstetrics should familiarize themselves with some particular method in their prognostication of what is going to happen to that woman and that baby. For example, in cases where the lead is low in the pelvis and freely movable at term, we are justified in believing that that baby will be delivered spontaneously or with ordinary forceps.

If I were limited to only one x-ray picture I would certainly prefer the lateral view. One reason is that you get a better view of the pelvic inclination, as Dr. Jacobs has frequently mentioned. Another reason is that the head is in practically the same plane as the true conjugate, so that you do not have the distortion due to differences in magnification, on account of the distance from the x-ray machine to the plate.

Obstetrical patients fall into one of three classes: One, the cases where we can see at a glance that there is plenty of room; another, where we can see from the x-ray examination that it is a questionable case; and third, the cases in which we can tell definitely that there is marked disproportion. In the cases where there is plenty of room and in those with marked disproportion, we need have little concern about what to do. It is to the group with relative disproportion that thought must be given. It is very simple to take an ordinary lateral plate and with the centimeter rule measure the longest diameter of the head and the true conjugate. If the outlet is normal and you have from 1 to 3 cm. less on the long diameter of the head than you do on the true conjugate, you can feel sure that everything is all right.

DR. A. N. CREADICK, NEW HAVEN, CONN.—This paper establishes the fact that the old-fashioned external measurements, and even the true conjugate, are of limited value as compared with such facilities as are here described. The lateral film does not, of course, preclude the use of other films. This film, for example, does not permit a study of asymmetrical contractions of the inlet.

The exact technique employed is not important, but the point is that the obstetrician must at once get in touch with his x-ray technician and work out a simple means of performing these examinations. These are done, not to eliminate abdominal palpation, and the other examinations, but to serve as an adjunct to them. With the lateral view alone, the passageway is not completely pictured, but Dr. Jacobs has done remarkably well in calling your attention to the various interesting minor variations that play such an important part in the function of that passageway.

DR. JACOBS (closing).—Dr. Cosgrove shows more concern regarding pelvic classification and the use of stereoroentgenograms than I do. Although it must be conceded that these factors are of value, in my mind they are not as practical, from the point of view of expense and routine application, as the procedures I have advocated. I have in particular directed attention to what may be done with limited finances and facilities, such as exist in any large clinic, and the favorable results obtained.

We realize that the "available true conjugate" which is 0.7 cm. less than the true conjugate, is the determining diameter as far as engagement is concerned. Yet this was not emphasized in the manuscript, because all authors and almost all clinicians use for both reference and comparisons the true conjugate.

Dr. Cosgrove stated that the prediction of prognosis in the "guarded," "test labor," and "cesarean section" groups was not specific as in the "favorable" group. In this respect I would reply that the percentage of accuracy in prognosticating is not the ultimate purpose of such study. The idea is to classify the case in the appropriate group so that the patient can receive proper consideration.

Of course there are other factors, as suggested by Dr. Creadick, that are important, such as type of uterine contractions, behavior of cervix, etc. But I still think that the most important factor is the bony pelvis, and usually the most important part is the plane of the inlet, and the most important diameter is the true conjugate.

Although the application of roentgenographic study is an adjunct to obstetric management, it is as far as I know the most important one that we have, and is particularly intended for borderline cases.

This presentation was prepared for three purposes:

1. To show that Smellie's rule is invalid.
 2. To emphasize that roentgenographic interpretation, by a simple technique, should be available in all borderline cases.
 3. To show that the vast majority of borderline cases, if properly studied, may be treated conservatively.
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OCCIPUT POSTERIOR—A NORMAL PRESENTATION*

L. A. CALKINS, M.D., PH.D., KANSAS CITY, KAN.

(From the Department of Obstetrics and Gynecology, Kansas University Medical School)

IN A PREVIOUS publication,¹ I stated that occiput posterior occurs almost as frequently as occiput anterior. It does not produce a significant increase in either maternal morbidity or fetal mortality. Spontaneous internal rotation can be as confidently expected in the posterior position as in the anterior one. Operative delivery is necessary in about the same proportion of cases. In one respect only is occiput posterior different from occiput anterior. The first stage of labor is one to two hours longer and the second stage longer by a few minutes only.

Further careful observation has not changed these previous conclusions except in one respect. We have recently discovered that occiput posterior does not lead to a longer first stage of labor. In that one respect our previous statement was not correct. We can now say that the only difference between occiput posterior and occiput anterior is that of a few minutes in the duration of the second stage of labor.

In this presentation we shall try to show (1) why the first stage of labor is of the same duration in occiput posterior as in occiput anterior and (2) we shall try to determine the reasons for the difference in duration of the second stage.

FIRST STAGE

In a recent study² of a considerable series of patients seen at the very onset of labor, it has been possible to predict the duration of the first stage on the basis of the relative degree of effacement of the cervix, the consistency of the cervix, the station of the presenting point, and the character of the labor pains. Other factors, previously considered important, were shown to be negligible in importance, and, of these four factors, station is much less important than the other three. It was found that those primiparas entering labor without complete effacement of the cervix had labors about three hours longer than those whose cervixes were effaced when labor began. A relatively firm cervix (of

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

the consistency of the ala of the nose) resulted in labors about three hours longer than those with softer cervices (of the consistency of the lip). Those primiparas who had good pains (a frequency of three minutes or less with at least fair intensity) at the beginning of the dilatation phase would exhibit, under otherwise ideal conditions, a first stage of about three hours. Those whose pains were only fair (of either poor intensity or longer frequency, but not both) would require about six hours to complete their dilatation. Poor pains (of both a weak intensity and long interval) under otherwise favorable conditions needed some twelve hours to bring about dilatation.

These above factors were found to be quite constant in individual patients. Two conditions only affect one's ability to predict the duration of labor on the basis of these findings. Occasionally a patient will enter labor with an uneffaced cervix and will spend long hours in the effacement process to be followed by rather good pains during the dilatation phase. This is unusual. Ordinarily where the pains are very poor and infrequent during the effacement period, they will also be poor and infrequent during the dilatation period. In the second place, one will occasionally observe secondary inertia beginning at 6 or 8 cm. dilatation in a patient whose pains have been previously good and whose progress has been correspondingly rapid. This also is unusual and was observed only three times in the present series of over one thousand patients. Ordinarily, secondary inertia occurs in patients whose pains have previously been poor and whose progress has correspondingly been slow.* If, then, all of the usual variations in labor can be explained on the basis of cervix, station, and labor pains, some explanation becomes necessary for the apparently longer first stage of occiput posterior.

Table I shows the twelve groups (according to cervix and labor pains) with the incidence of occiput anterior and occiput posterior in each group along with the average duration of the first stage of labor in hours and minutes. The consideration of station was omitted as to have included it would have doubled the number of groups and added little to the clearness of the exposition. In 9 of the 12 groups, occiput posterior had a shorter duration of the first stage than occiput anterior. In the remaining 3 groups, occiput posterior showed a longer duration. In several of these groups the number of cases is quite small which, we be-

*Much of our present conception of the possible difficulty to be encountered with occiput posterior has come from careful observation of just the second stage of labor in individual patients where difficulty has arisen. Where similar difficulty has arisen in the second stage in occiput anterior, we have perhaps ascribed that difficulty to its real cause, as occiput posterior was not present and could not be blamed. We have also failed to take cognizance of the fact that the second stage of labor is an entirely different process than the first stage of labor and that the first stage is governed by different factors, some of which are not present at all in the second stage. Some of our misconceptions of the first stage of labor have arisen from the fact that we do not see our patients until after they have been in labor for some hours and part of the process has already been completed. We cannot then know the status which was present at the beginning of their labors. This recent group of patients were all seen at the very onset of their labors and the conditions present at that time accurately recorded.

TABLE I. PRIMIPARAS, FIRST STAGE

CERVIX	PAINS	OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
Effaced, soft	Good	103 Pt., 3 hr. 57 min.	51 Pt., 3 hr. 41 min.
Effaced, firm	Good	17 Pt., 4 hr. 36 min.	7 Pt., 4 hr. 30 min.
Not effaced, soft	Good	65 Pt., 6 hr. 13 min.	48 Pt., 6 hr. 03 min.
Not effaced, firm	Good	14 Pt., 8 hr. 25 min.	21 Pt., 7 hr. 43 min.
Effaced, soft	Fair	38 Pt., 7 hr. 04 min.	32 Pt., 6 hr. 43 min.
Effaced, firm	Fair	16 Pt., 10 hr. 34 min.	17 Pt., 10 hr. 51 min.
Not effaced, soft	Fair	49 Pt., 8 hr. 00 min.	49 Pt., 10 hr. 19 min.
Not effaced, firm	Fair	15 Pt., 14 hr. 10 min.	20 Pt., 12 hr. 32 min.
Effaced, soft	Poor	17 Pt., 16 hr. 04 min.	23 Pt., 13 hr. 24 min.
Effaced, firm	Poor	7 Pt., 16 hr. 16 min.	9 Pt., 19 hr. 37 min.
Not effaced, soft	Poor	13 Pt., 23 hr. 45 min.	23 Pt., 17 hr. 46 min.
Not effaced, firm	Poor	12 Pt., 25 hr. 15 min.	15 Pt., 21 hr. 59 min.

lieve, accounts for the discrepancy of hours between occiput anterior and occiput posterior, as it is our present belief that occiput posterior does not have a shorter first stage than occiput anterior nor a longer first stage, but an identical first stage under like conditions of effacement, consistency of the cervix, and character of labor pains.* (Absolute accuracy should include a consideration of station also.)

Table II shows the similar data for multiparas. Here we find six groups where the occiput posterior labor averaged slightly longer, four groups where it is less, and one of equal length. The number of patients in this multiparous series is so small as to be inconclusive.

We would like particularly to call attention in Table I to the tendency of occiput posterior to be associated with unfavorable conditions of uneffacement and firm consistency of the cervix and also the relatively greater proportion of occiput posterior patients whose pains are only fair or actually poor. One might debate as to whether occiput posterior tended to result in poor pains, or firm or uneffaced cervix. Such statements have been made by some observers. Potter has, on the other hand, suggested that possibly all labors start as occiput posterior,

TABLE II. MULTIPARAS, FIRST STAGE

CERVIX	PAINS	OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
Effaced, soft	Good	43 Pt., 2 hr. 4 min.	27 Pt., 2 hr. 14 min.
Effaced, firm	Good	5 Pt., 2 hr. 40 min.	1 Pt., 2 hr. 15 min.
Not effaced, soft	Good	44 Pt., 3 hr. 38 min.	35 Pt., 3 hr. 39 min.
Not effaced, firm	Good	10 Pt., 4 hr. 45 min.	8 Pt., 4 hr. 32 min.
Effaced, soft	Fair	18 Pt., 4 hr. 40 min.	17 Pt., 4 hr. 19 min.
Effaced, firm	Fair	3 Pt., 4 hr. 3 min.	1 Pt., 4 hr. 10 min.
Not effaced, soft	Fair	31 Pt., 5 hr. 43 min.	26 Pt., 6 hr. 16 min.
Not effaced, firm	Fair	8 Pt., 8 hr. 43 min.	10 Pt., 8 hr. 01 min.
Effaced, soft	Poor	8 Pt., 5 hr. 25 min.	5 Pt., 6 hr. 00 min.
Effaced, firm	Poor	0 Pt., - hr. - min.	0 Pt., - hr. - min.
Not effaced, soft	Poor	11 Pt., 9 hr. 27 min.	16 Pt., 10 hr. 08 min.
Not effaced, firm	Poor	4 Pt., 11 hr. 23 min.	2 Pt., 16 hr. 40 min.

*A study of attitude is in progress and will be submitted later.

and we might reason that early rotation to an anterior position is the result of a favorable cervix and good labor pains. Whatever one's belief may be, these data show that more than 150 occiput posterior patients, under favorable conditions of cervix and pains, had very short labors, whereas none of the patients with occiput posterior or occiput anterior with unfavorable conditions of cervix and pains had short labors. The 49 patients with occiput anterior with poor pains had an average first stage of twenty hours and twenty-three minutes, and the 70 patients with occiput posterior with poor pains had an average first stage of seventeen hours and twenty-eight minutes. This would suggest that possibly occiput posterior was even more favorable than occiput anterior under these circumstances. We do not believe this to be true; we do believe, however, that occiput anterior and occiput posterior will have a first stage of the same duration under exactly similar conditions of cervix and labor pains.

SECOND STAGE

When one attempts to analyze the various factors involved in the second stage of labor, one encounters certain forces and resistances which do not lend themselves readily to measurement. The voluntary effort of the patient, of course, varies widely, but we have not, as yet, known how to apply any measurement or estimate of the relative value of this voluntary effort in a given patient. It is almost totally lacking in some patients while in others it is of greater import than the involuntary contractions of the uterus. This is particularly true in multiparas, but is also observed infrequently in primiparas. The resistance offered by the pelvic floor and vulva is also rather difficult to measure. In a previous publication,³ we pointed out that large babies resulted in a longer average second stage than was necessary for the medium and smaller sizes. This factor was negligible in multiparas but was a definite quantity for primiparas.

In the present comparison of occiput posterior and occiput anterior, only two other variables were analyzed: first, the labor pains; and, second, the time of internal rotation. Labor pains were said to be good (for purposes of this study) when they were of strong intensity or were of fair intensity and not more than two minutes apart. They were said to be poor if they were of very weak intensity or if they were of fair intensity but at an interval greater than two minutes.

Inasmuch as one of the principal differences between occiput posterior and occiput anterior is in the degree of internal rotation necessary, we made it a point to study internal rotation in some detail, noting when it occurred with respect to both the first and second stages of labor and also when it occurred relative to station in the pelvis. In a previous publication, we had already pointed out that the percentage of spon-

taneous internal rotation in occiput posterior was the same as for occiput anterior. We also indicated that more than one-third of either group did not exhibit internal rotation until after the pelvic floor had been reached. In the analysis which follows, the term "rotated" is applied to those patients where internal rotation takes place before or at the moment that the presenting point reaches the pelvic floor. "Unrotated" is applied to those cases where rotation takes place on the pelvic floor or delivery occurs without internal rotation.

The presenting point reaches the pelvic floor before or at about the same time as dilatation is completed in about one-half of all patients. There is no "descent" phase of the second stage in these patients. In the remaining half, the head may be at a variable distance above the pelvic floor at the time of completion of dilatation, and anywhere from a few minutes up to one-half hour or more may elapse before the presenting point reaches the pelvic floor. In these patients the same "pelvic floor" phase must then ensue. Obviously this second group of patients will have a second stage considerably longer in comparison than the other group and, therefore, cannot be compared directly. We have chosen, therefore, to divide the second stage into the two phases of "descent" and "pelvic floor" in this comparison of occiput posterior and occiput anterior. Table III for primiparas and Table IV for multiparas will present the data according to this plan. (These are the spontaneous deliveries; operative deliveries are treated in Table V.)

TABLE III. PRIMIPARAS, SECOND STAGE

PAINS			OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
Descent	Good	Rotated	211 Pt., 12.9 min.	170 Pt., 13.9 min.
	Good	Unrotated	104 Pt., 11.8 min.	84 Pt., 13.8 min.
	Poor	Rotated	79 Pt., 25.6 min.	54 Pt., 27.4 min.
	Poor	Unrotated	56 Pt., 21.5 min.	48 Pt., 34.8 min.
Pelvic floor	Good	Rotated	380 Pt., 33.3 min.	304 Pt., 37.6 min.
	Good	Unrotated	213 Pt., 37.9 min.	158 Pt., 49.2 min.
	Poor	Rotated	118 Pt., 55.0 min.	98 Pt., 60.8 min.
	Poor	Unrotated	96 Pt., 60.5 min.	78 Pt., 81.5 min.

TABLE IV. MULTIPARAS, SECOND STAGE

PAINS			OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
Descent	Good	Rotated	156 Pt., 7.2 min.	96 Pt., 7.6 min.
	Good	Unrotated	67 Pt., 5.8 min.	55 Pt., 9.7 min.
	Poor	Rotated	37 Pt., 14.1 min.	37 Pt., 16.2 min.
	Poor	Unrotated	30 Pt., 13.5 min.	30 Pt., 17.8 min.
Pelvic floor	Good	Rotated	310 Pt., 11.5 min.	198 Pt., 12.8 min.
	Good	Unrotated	133 Pt., 12.4 min.	111 Pt., 15.2 min.
	Poor	Rotated	69 Pt., 20.2 min.	55 Pt., 16.5 min.
	Poor	Unrotated	59 Pt., 23.2 min.	52 Pt., 30.0 min.

THE DESCENT PHASE

The descent phase of the second stage in occiput posterior is not strikingly different from in occiput anterior. Where rotation occurs during descent (about two-thirds of all patients), the difference in time between occiput posterior and occiput anterior is not over one or two minutes. On the other hand, where descent occurs without internal rotation, the difference may be more marked. If the pains are good, the differential is apparently a matter of two or three minutes only. In the presence of poor pains, the difference in multiparas is about four minutes. In primiparas, whose pains were poor, there were:

	OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
Medium-sized babies	45 Pt., 23.7 min.	34 Pt., 29.6 min.
Large babies (over 3,500 Gm.)	16 Pt., 22.0 min.	15 Pt., 42.7 min.

The number of patients observed in each of these groups is so small that no definite conclusion should be drawn. It seems unlikely, however, that as much as twenty minutes' difference exists between occiput anterior and occiput posterior even under the unfavorable conditions of poor pains, large babies, and lack of internal rotation.

There were altogether eight instances of failure of descent, 2 occiput anterior and 6 occiput posterior. In only one instance were the pains of even fair intensity and frequency. In three instances the pains were so weak and so far apart that labor could almost be said to have ceased altogether. In only two instances was the baby very large (3,885 Gm.; 4,035 Gm.). Moderate deflexion of the head was present in two cases. The occiput posterior position was thought to have contributed to the failure of descent in two or possibly three of these cases.*

THE PELVIC FLOOR STAGE

In the pelvic floor or expulsion phase, one notes a consistently present difference between occiput anterior and occiput posterior. Even in the presence of good pains with the head completely rotated occiput posterior will require from three to six minutes more in the expulsion phase. Oddly enough the same difference was observed when the pains were poor: One would expect that the completely rotated occiput posteriors might be exactly like completely rotated anteriors. That such is not the case can possibly be explained by imperfect dispersion of the expulsive forces on the markedly rotated head. When rotation occurs after the head reaches the pelvic floor or fails to occur, those patients delivered

*One of these six posterior cases had completely rotated and was delivered after sixty-one minutes of second stage pains by median forceps. The baby weighed 4,035 Gm. In another, manual rotation and median forceps after 290 minutes (thought to be due to injudicious use of twilight sleep) delivered a baby weighing 3,300 Gm. No. 3. Median forceps rotation and delivery after seventy-four minutes (3,150 Gm.). No. 4. Median forceps rotation and delivery after 130 minutes (3,885 Gm.). No. 5. Median forceps rotation and delivery after 100 minutes (3,870 Gm.). No. 6. Median forceps delivery without rotation, 100 minutes (3,110 Gm.). The two occiput anteriors were delivered by median forceps rotation and extraction, one after eighty-three minutes (3,430 Gm.) and one after 155 minutes (2,770 Gm.).

spontaneously will show an average difference of eight to twelve minutes if the pains are good and fourteen to seventeen minutes when the pains are poor. The longer are of internal rotation would seem to be a partial explanation for this time difference.

Failure of internal rotation in the time allotted (the length of time varied according to our clinical judgment in the individual patient) was observed nineteen times in the occiput anterior primiparas (2 per cent). The importance of this datum was not recognized early in the study, and we probably failed to observe several additional instances in the occiput anterior cases. Failure of rotation in the occiput posterior primiparas was observed forty-six times (5.9 per cent). In exactly half of these patients (23), spontaneous delivery took place with the occiput posterior and with an average pelvic floor phase of sixty-six minutes. Five of the persistent occiput anteriors also delivered spontaneously without rotation. This left a remainder of 14 unrotated occiput anteriors and 23 unrotated occiput posteriors to be delivered by operative procedure. This intervention was thought necessary after an average of one hundred minutes for the occiput anteriors and one hundred twenty-five minutes for the occiput posteriors. Whether the failure of these two groups of 14 and 23 patients to deliver spontaneously in the time allotted should be ascribed to poor labor pains, or to failure of rotation, or to oversized baby, or to moderate degrees of extension of the head, or to all of these causes combined, we cannot yet say as the number of patients available for study is far too small from which to draw exact conclusions. The only positive statement is that an increased operative incidence of nine (or ten) in a series of 780 occiput posterior primiparas was observed in this series.

That operative delivery was not otherwise more frequent for occiput posterior than for occiput anterior is well shown in Table V.

TABLE V. PRIMIPARAS, OPERATIVE DELIVERY

	OCCIPUT ANTERIOR	OCCIPUT POSTERIOR
<i>Good Pains</i>		
Maternal and fetal distress	13 Pt., 21.2 min.	13 Pt., 33.5 min.
Lack of progress { Rotated	28 Pt., 60.3 min.	19 Pt., 65.3 min.
Unrotated	3 Pt., 106.0 min.	2 Pt., 98.5 min.
<i>Poor Pains</i>		
Maternal and fetal distress	13 Pt., 39.6 min.	10 Pt., 26.4 min.
Lack of progress { Rotated	62 Pt., 99.4 min.	63 Pt., 93.6 min.
Unrotated	11 Pt., 98.1 min.	21 Pt., 127.3 min.
Total patients in series	955	780

In summary then, the second stage in occiput posterior can be said to be as much as thirty-five minutes longer for occiput posterior, depending upon the associated factors of labor pains, infant size, station at which dilatation is completed, and the time at which internal rotation

takes place; operative intervention was, in our judgment, necessary in this series in 1 per cent more instances than was thought necessary for occiput anterior.

CONCLUSIONS

1. The first stage of labor is dependent upon the condition of the cervix and the character of the labor pains, and is not different for occiput posterior from that for occiput anterior.

2. The second stage of labor in occiput posterior presents more work to the expulsive forces in order to rotate the head through the necessarily greater arc as represented by a time difference of two to thirty-five minutes in primiparas. Part of this time difference may, however, be the result of the (greater arc of rotation of the head on the body and consequent) misdirection of expulsive force.

3. Our clinical judgment dictated the use of low forceps in (unrotated) occiput posterior more frequently than in occiput anterior; 10 additional instances in 780 occiput posteriors.

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DISCUSSION

DR. R. T. LAVAKE, MINNEAPOLIS, MINN.—Experience, I believe, shows that, given equal degrees of deflexion, the length and difficulties of labor would vary in the first stage according to the character of the pains, the condition of the cervix, and to some extent to the station of the head; in the second stage according to the character of the pains, the station of the head, and the need of rotation.

Realizing that accurate measurements of degrees of deflexion, even if possible, would complicate his investigation tremendously, Dr. Calkins has relied upon a fortuitous averaging of this factor of deflexion. He has limited himself to factors that lend themselves to more accurate mensuration and tabulation.

Experience has, however, taught that under equal conditions of cervix and uterine contractions, the length of labor will vary directly with the degrees of deflexion present. If one is inclined to question this generalization, let him compare the length of labor of a few frontocotyloid attitudes or a few brow presentations, with a like number of well-flexed heads in either anterior or posterior positions.

Now the figures in Dr. Calkins' paper demonstrate that, with the same conditions of the cervix and of pains, the length of labor was approximately the same in the two groups of anterior and posterior positions. This equality in length of labor can only be interpreted as showing that in these samples, the average degrees of deflexion happened to be approximately the same. Had the average of deflexion been unequal, the average length of labors would not have been equal.

It is not surprising that Dr. Calkins' previous report, that he mentions, and the present report differ as to the lengths of labor. These differences are merely due to the differences in the averages in these two samples, of the hidden factor, deflexion. If we did not know accurately the comparative amounts of deflexion, we would not be in a position to argue that posterior positions are no more to be feared than anterior positions. To so argue would be to commit what is known in logic as the fallacy of neglected aspect.

It is interesting that they show a tendency for greater length of labor in the posterior positions, because this would tend to confirm the opinion held by most of us, I believe, that in both theory and practice the potential for deflexion is greater in posterior than in anterior positions.

DR. J. BAY JACOBS, WASHINGTON, D. C.—In the vast majority of cases, as demonstrated by roentgenography, the head has a tendency to engage with the biparietal diameter in the true conjugate. The character of the pelvic floor, type of labor pains, pelvis and so on, will determine whether the occiput will rotate anteriorly or posteriorly.

Certain authors (as Danforth) state that 70 per cent of primary occipitoposteriors will rotate anteriorly, while certain others think that 90 per cent will rotate. That more than 90 per cent can rotate anteriorly has been shown by Dr. Calkins, who appears to be very conservative. Of course, the men who claim that only 70 per cent will rotate anteriorly generally interfere earlier. At times it does pay to interfere in an occiput posterior, because I, personally, feel that labor, particularly in the persistent type, takes much longer than in the anterior variety.

A prolongation of only twenty minutes of the second stage in the group where circumstances were shown to be unfavorable, may be misinterpreted. It would take only two or three persistent posteriors to make that much difference in a large series of cases.

Dr. Calkins has been very fortunate in his series of cases to have had only three in 1,000 in which we may say that progress of labor stopped after the cervix was only a few centimeters dilated. Persistent occiput posterior offers me a lot more concern than seems to be the present general attitude.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—I would like to ask Dr. Calkins if any of these cases had been subjected to analgesia during the first and second stages. His average time for the whole succession of events, which he recognizes in his report, seems very short as compared with my own experience. I wonder if part of the difference is due to the fact that analgesia has been entirely eliminated in his study of the mechanism of labor?

DR. B. H. CARROLL, TOLEDO, OHIO.—Were the patients all kept in bed, or were some of them allowed to get up and move around? If the latter, were abdominal binders or something of that sort used?

DR. CALKINS (closing).—We are conducting a similar study on the question of deflexion, but we do not yet have definite conclusions. I had in the beginning exactly the same impression as Dr. LaVake concerning the deflexion attitudes. I have not yet been convinced that that impression is wrong, but I think that perhaps deflexion represents a state of unpreparedness for labor, just as occiput posterior may represent a state of unpreparedness for labor. A deflexion attitude would perhaps not exist except for the fact that the lower uterine segment is not stretched out, the cervix is not effaced, and the state of tonicity is not satisfactory. I think it may be the result rather than the cause.

There is something more than just coincident equality of deflexion between the occiput anteriors and occiput posteriors in this series. Perhaps I did not clearly point out that in the previous series where we did recognize a difference in time between occiput posterior and occiput anterior, we did not realize the more frequent association of firm cervixes and poor labor pains with occiput posterior. This time we have recognized that association and we have therefore completely altered our previous conception that posterior occiput does make for a long labor. I would like to repeat that under like conditions of cervix and labor pains the length and ease of the first stage of labor are exactly the same for posteriors and anteriors.

We recognize as the end of the first stage of labor the time when the cervix can no longer be felt by rectal or vaginal examination. We had only four or five instances in this whole series, where the second stage was as much as two and one-half hours long.

Misceconception about the second stage of labor has been due in part to the fact that men have regarded the first stage as ended when they decided that the cervix was sufficiently dilated to let the head come through. We insist on waiting until the cervix cannot be felt. The minute the cervix ceases to be the determining influence there is much more rapid progress. Our second stage is shorter because we determine the beginning of the second stage differently.

Our patients have plenty of analgesia, sometimes a little too much. As for the first-stage analgesia, in my private patients, I start giving nitrous oxide in analgesic doses as soon as the pains become at all hard. We do not use any other analgesic except morphine, when it seems to be indicated. I cannot say what proportion of patients receive morphine. It is given on indication.

TRANSVERSE PLICATION OF THE RECTUM FOR THE REDUCTION OF LARGE RECTOCELES*

WALTER T. DANNREUTHER, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)

A POSTOPERATIVE protrusion through the vulvar orifice after a vaginal operation is a disappointment to the patient and embarrassing to the operator. Inversion of the vagina after hysterectomy, recurrence of prolapse after an interposition or Manchester operation or a colpectomy, and the reappearance of a cystocele after colporrhaphy, can usually be attributed to faulty surgical technique. Persistent distention of the posterior vaginal wall, following various plastic procedures, is sometimes due to the presence of an overlooked enterocele in the cul-de-sac which should have been corrected. On the other hand, there are some cases of lacerated perineum associated with a large rectocele, for the cure of which a perineorrhaphy alone is entirely inadequate, despite the absence of a true posterior vaginal hernia. The chief anatomic defect in a perineum damaged by birth trauma lies in the impairment of its muscular integrity, particularly a diastasis of the vaginal fibers of the levator ani, and a satisfactory surgical repair depends upon the proper restoration of the perineal body, regardless of the mucous membrane incisional design. When, however, there is a coexisting large and high rectocele, it is equally as necessary to dispose of the redundancy in the rectal wall as to repair the damage sustained by the perineal musculature. Otherwise, the bulging rectum may again

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

overstretch the mucosa of the posterior vaginal wall and present itself at the vaginal orifice. The reduction in size of the dilated rectum is usually accomplished by plicating the anterior wall on its longitudinal axis, and then reinforcing the first suture line by a superimposed approximation of the pararectal tissues. This method really fails to take up the slack in the atonic longitudinal muscle fibers in the rectal wall and incidentally narrows its lumen. It, therefore, seems much more logical to infold the rectal wall on its transverse axis, thus affording the muscle fibers an opportunity to regain their lost tonicity, and preserving the normal caliber of the rectal canal. For many years I have

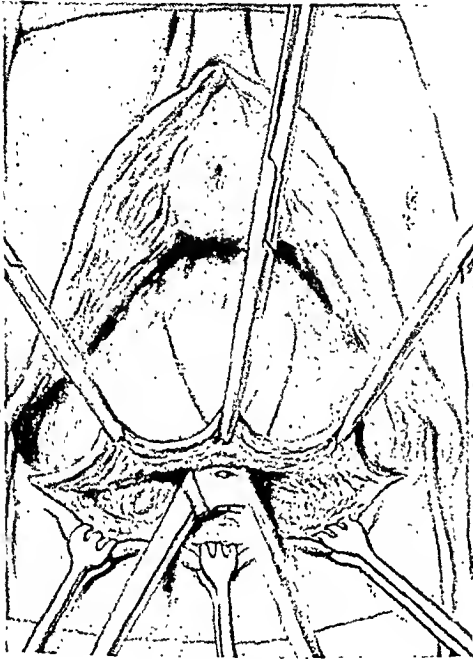


Fig. 1.

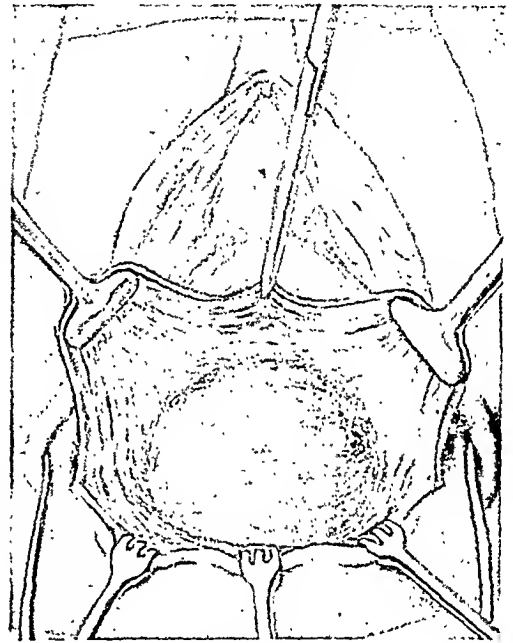


Fig. 2.

Fig. 1.—Transverse incision and separation of the vaginal and rectal walls.
 Fig. 2.—Free mobilization of the rectocele.

utilized such a procedure with gratifying results, and venture to describe it in detail without any pretense of originality. I can only say that I have not read a description of the technical steps elsewhere or seen any other operator in this country or abroad dispose of a rectocele in the same way.

METHOD

The fourchette is incised transversely and the lower margin of the wound grasped with three tenaculum clamps. At the same time, an assistant applies three Ochsner clamps at opposite points on the edge of the vaginal mucous membrane. A curved Mayo scissors is then thrust between the posterior vaginal wall and the anterior rectal wall to the apex of the rectocele (Fig. 1). By widely separating the blades of the scissors, the vagina and rectum are easily and bloodlessly detached

from each other. After removing the Ochsner clamps, the vaginal mucous membrane is cut in the midline with straight seissors to the upper limit of the rectocele. The angle of the incision is elevated with an Ochsner clamp and the margins of the two mucous membrane flaps

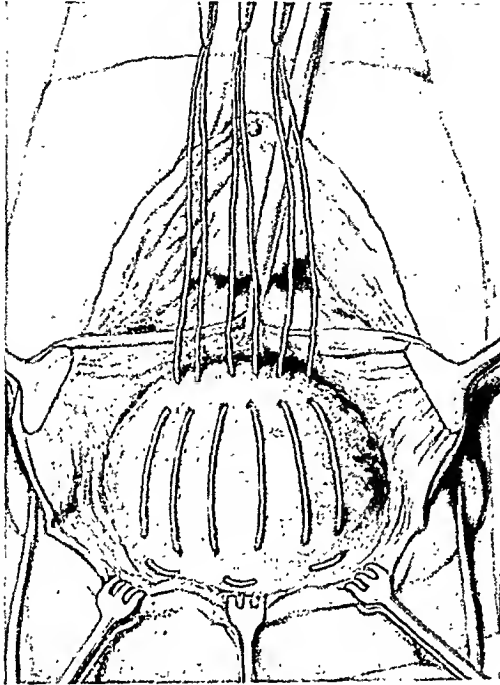


Fig. 3.—Placing the three Pagenstecher linen sutures.

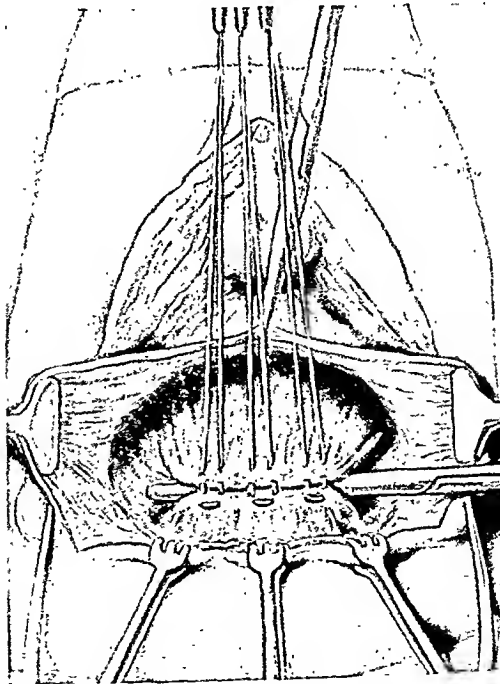


Fig. 4.—Infolding the rectal wall after pulling the mattress sutures taut.

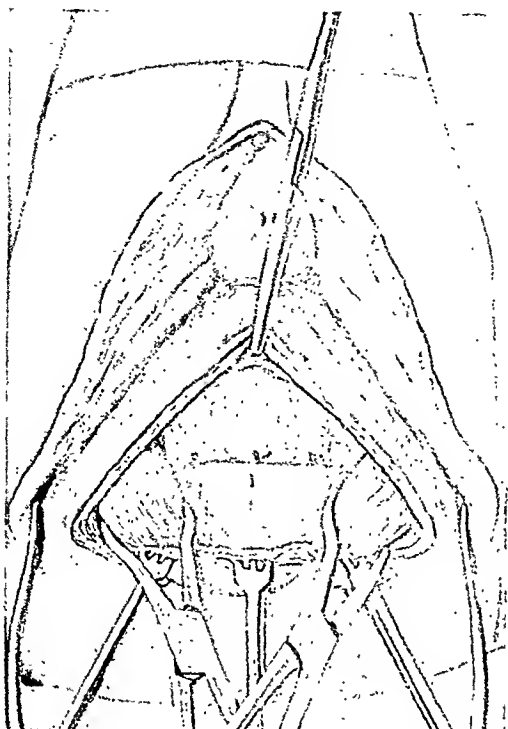


Fig. 5.—Elevation of the vaginal fibers of the levator ani with their overlying fascia.

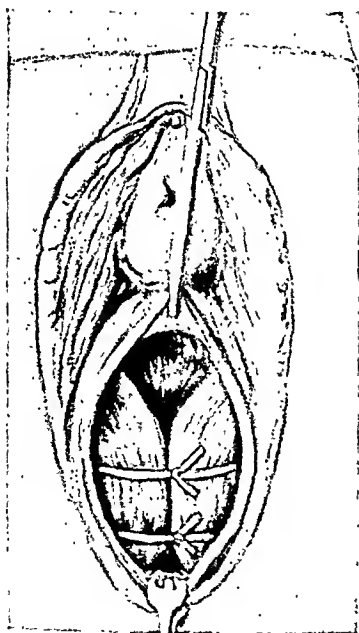


Fig. 6.

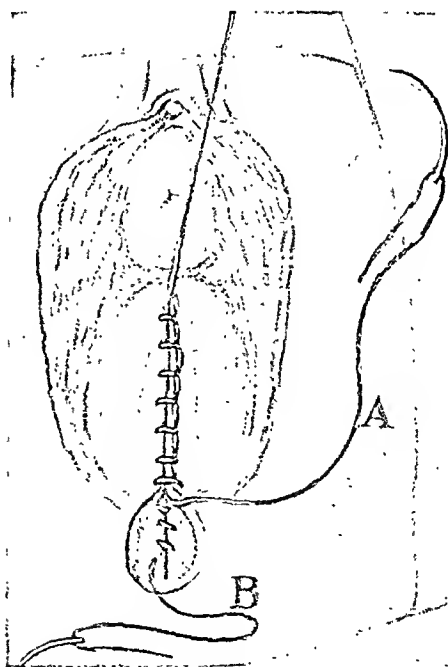


Fig. 7.

Fig. 6.—Approximation of the levator ani muscles with two encircling kangaroo sutures.

Fig. 7.—The interlocking chromic catgut suture (A) is laid aside while the perineal fascia is closed with a running chromic suture (B), and then used again to close the perineal skin with a few subcuticular bites.

with T clamps (Fig. 2). The bulging rectum is then freely mobilized laterally by means of gauze covered finger dissection, and the separated vaginal fibers of the levator ani muscle with their overlying fascia exposed in the same way. After fastening the handles of the T-clamps to the patient's buttocks on each side with towel clamps, three Pagenstecher linen mattress sutures are placed in the rectal wall from above downward, leaving them quite loose and holding their long ends temporarily with clamps (Fig. 3). An assistant inserts a hemostat or other straight instrument transversely beneath the slack sutures, and infolds the rectal wall evenly before the three sutures are pulled taut simultaneously (Fig. 4). As the first one is tied, the assistant slips the tip of the hemostat from underneath it, again from under the one in the midline, and finally withdraws it completely as the third one is knotted. The excess of vaginal mucous membrane on each side is then cut away, leaving a triangular area to be closed. The rectum is guarded by a finger as the assistant makes traction on one of the lateral tenaculum clamps to expose the fascia covering the levator ani fibers on that side. These structures are picked up in a towel clamp, and the same steps are carried out on the opposite side (Fig. 5). The separated muscle fibers are then encircled with two or more medium-sized kangaroo tendon sutures which are tied sufficiently tight so that the muscles are approximated in the midline without strangulation (Fig. 6). Before the ends are cut, the vaginal orifice is tested to see that it will comfortably accept the introduction of two fingers. The margins of the vaginal flaps are brought together with an interlocking continuous chromic catgut suture, which starts at the upper angle, picks up the rectal wall in its first bite, and is continued down to the fourchette. This suture is then laid aside, while the perineal fascia is closed with another chromic running suture (Fig. 7), after which it is used again to close the perineal skin with a few subcuticular bites. A strip of iodoform gauze is placed in the vagina, and a dry vulvar pad applied. The gauze is removed after forty-eight hours and the perineum kept dusted continuously with thymol iodide. No douches are allowed. An enema is given on the third day, and bowel movements permitted thereafter.

I have done this operation with uniformly satisfactory end results, except in one case in which I carelessly neglected to include the rectal wall in the first bite of the suture starting at the upper angle of the vaginal wound. This patient developed a small prolapse of the rectum through the anus, which was easily reduced. Incidentally, these technical steps seem to contribute materially to the early restoration of bowel function.

580 PARK AVENUE

DISCUSSION

DR. LOUIS E. PHANEUF, BOSTON, MASS.—It is admitted that a myorrhaphy of the levators or an ordinary reconstruction of the perineum will not overcome a large rectocele. Longitudinal plication of the rectum may work satisfactorily in the lesser degrees of rectocele, but very unsatisfactorily in the large rectoceles.

In July of this year I had occasion to use this procedure for the first time in an extremely large rectocele. In this case I first opened the cul-de-sac of Douglas

to rule out an enterocele. The rectocele itself was of such size that I had to plicate the rectum in three layers, but the result was highly satisfactory.

DR. EMIL NOVAK, BALTIMORE, MD.—The procedure advocated is certainly much more conservative than one suggested many years ago of actually resecting the redundant portion of the rectum in cases of very large rectocele. On the other hand, I feel that even Dr. Dannreuther's procedure should rarely be necessary, because of the strong tendency of the redundant bowel to involute and regain its normal caliber once the rectocele has been properly corrected.

Both Dr. Dannreuther and Dr. Phaneuf have emphasized the futility of the ordinary outlet repair, with simple approximation of the levator muscles, in the correction of the large rectocele which often involves the entire rectovaginal septum, representing a hernia of the rectum through the latter. When simple perineorrhaphy is done in such cases, the patient is quite sure to return with the large rectocele bulging into or out of the vagina over the margin of the united levators. The rectovaginal septum, however, can be satisfactorily and easily restored by one of various techniques, depending partly on individual indications and partly on the preference of the operator.

A useful technique, which I frequently employ, is that suggested many years ago by Dr. George G. Ward and Dr. Albert Spalding, quite independently. By this method the rectum is elevated and rotated on its transverse axis upward toward the pelvis, accomplishing essentially the same result as Dr. Dannreuther's procedure. In other cases the septum can be restored by transverse approximation of the vaginal fascia which is continuous with the levator fascia. Whenever possible we should avoid techniques which involve placing sutures through the rectal wall itself, because of the theoretical possibility of an occasional rectovaginal fistula. This was a fault of the original Ward-Spalding technique which subsequent modification has eliminated.

DR. JAMES W. KENNEDY, PHILADELPHIA, PA.—I have stated a number of times that repair of the perineum was a lost art and that over 60 per cent of the repairs of the perineum which we perform have had one or more previous attempts at repair, ending in failures.

In these large rectoceles the prerectal tissues bulge forward, producing an extensive hernia in the posterior vaginal wall. The muscular and fascial planes, upon which the stability in the repair of the perineum depends, have been so widely separated that it becomes necessary to reduce the hernia of the prerectal structures before the muscular and fascial tissues can be properly approximated. This, Dr. Dannreuther has done by his transverse plication of the prerectal tissues. I always reduce the large protruding mass by plication of the tissues with the use of fine silk sutures. I finish the repair of the perineum by interrupted mass sutures of silkworm-gut.

In many of these extensive posterior lacerations, I feel that failure occurs on account of the too early absorption of the suture material which has been used. After seventy-two hours much of the tensile strength of any absorbable material is lost, and as there is abnormal tension placed on the sutures following the repair of these extensive vaginal hernias, too often muscular and fascial retraction will take place before stable union occurs.

DR. A. D. CAMPBELL, MONTREAL, CANADA.—The principle in the repair of a large rectocele lies not only in the reconstruction of the perineum but in reconstructing the rectovaginal septum throughout its entire length. I can readily see how a form of intussusception might follow such an operation if not properly done, and for this reason I am rather doubtful as to the general employment of transverse

plication. I have always felt that a colossal rectocele is but the visible portion of an existing megacolon. The operation of plication as advised by Dr. Dannreuther appeals to me in the surgical treatment of those cases where the rectocele has reached tremendous proportions.

DR. DANNREUTHER (closing).—This operation is indicated only in cases of large rectoceles. After many years of experience with this procedure, I have never seen a subsequent rectovaginal fistula. Should one occur, it would be due to faulty technique.

MIDLINE EPISIOTOMY*

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(From the Division of Gynecology and Obstetrics, Henry Ford Hospital)

THE claim that midline episiotomy is more comfortable than medio-lateral constitutes a challenge. The impression is so prevalent that several texts express preference for the midlocation if satisfactory healing can be assured. It has been our experience that the midline is safer and more satisfactory than the other approach.

Strict adherence to all surgical principles is important in obstetrics. The employment of aseptic technique is indispensable. Sharp dissection of tissues, complete hemostasis, and careful apposition of tissues by non-constricting sutures remain pertinent points. Improvement in methods and the adoption of new ideas and materials to replace less valuable procedures mark the progress of the times. The fields of preoperative sedation and anesthesia are notable examples. Stay sutures embracing large volumes of tissue are gradually being discarded, and the trend is now toward the use of finer suture material.

Division of perineal structures by a sharp scalpel offers less tissue insult than the crushing effect of scissors. Contusion of tissues by blunt instruments is a source of pain. Such devitalized tissue margins offer a nidus for infection. Edema and swelling are natural companions. Less perineal scarring and more rapid healing are additional merits of sharp dissection.

Mass ligation of tissue with through-and-through sutures favors pocket formation with retention of old blood. This is particularly important because the perineum is a contaminated field and care must be taken to obliterate all dead spaces. Accurate anatomic apposition of tissues promotes the healing process and discourages the onset of infection.

The perfect suture material has never been developed. It has long been recognized that buried catgut is a tissue irritant, and for some

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

time it has been suspected that it is a factor in the dehiscence of episiotomy wounds. Suture material is constantly being improved. The recent standardization by the United States Pharmacopoeia is an important step in the right direction. For the first time this gives us an opportunity to compare accurately the results obtained by different observers. Adoption of the United States Pharmacopoeia standards by all manufacturers will facilitate further comparison.

We believe that adherence to each one of these surgical principles is fundamentally important in perineal surgery. Numerous authors have emphasized one or more of these points. The earliest writers on episiotomy advocated a knife-edge for making the episiotomy wound.

Rueker¹ has pointed out in a detailed history of episiotomy that the blunt-pointed bistoury was one of the first instruments used. Pieri² and Gillis³ have recently stressed to the obstetrician the importance of anatomic knowledge of perineal structures. Pieri,² Royston⁴ and others have called our attention to the use of fine catgut. Phaneuf⁵ has pointed out the importance of layer suturing. The edema and swelling of the perineum following episiotomy and repair are recognized by all as a source of discomfort. To accommodate for this edema a method using a continuous knotless suture for reconstructing the perineum has been outlined recently by Rueker.¹

We are in accord with the various procedures just cited but wish to emphasize the importance of using them all.

For several years we have been using smaller and smaller catgut with increasing satisfaction, and for the past three years we have used five-0 chromic catgut for repair of episiotomy wounds. All incisions are made with a scalpel. Small bites of tissue with complete hemostasis and accurate anatomic apposition of tissue is practiced. We wish to stress that we are presenting nothing new, but feel that the suture material, recently made available, efficiently adapts itself to improved obstetric care. A simple method is presented which, we believe, offers both objective and subjective improvement.

METHOD

The perineum is allowed to bulge before the episiotomy is elected. We prefer to wait for this stage for two reasons: First, an episiotomy may not be necessary; and second, the pressure of the presenting part thins the perineum and demarcates the structures. A sterile wooden tongue depressor is then slipped into the vagina between the presenting part and the perineum. Pressure is maintained on the fundus to keep the perineum bulging. With a sharp scalpel the incision is begun at the level of the transverse muscle bundle. The incision is continued through all the structures until the scalpel meets the tongue depressor. Care is taken to sever the vulvar ring and the fascia over the anterior and posterior surfaces of the transverse perineal and sphincter muscles.

The episiotomy is repaired after completion of the third stage. Small, round-pointed needles threaded with five-0 chromic catgut are used. The fascia layers are identified and brought together with interrupted sutures embracing small bites of tissue. Particular attention is given to the fascia over the transverse muscle bundle. Care is taken to preserve the triangular shape of the perineum. Complete hemostasis and obliteration of dead spaces are practiced. The vaginal mucosa and skin are closed with interrupted buried sutures.

The aftercare consists of drying the perineum with a sterile towel and protecting it with a sterile pad. A pitcher douche is given after defecation or voiding. If the bowels have not moved by the third day, an enema is given.

DISCUSSION

The efficiency of midline incisions was pointed out in 1918 by Pomeroy.⁶ That this site is the natural cleavage plane is stressed by the frequency of spontaneous lacerations in this location. Permanent injury to muscle fibers can be prevented by a well-timed midline episiotomy. The objection to midline episiotomy is the risk of extension into a third-degree laceration. The misfortunes of this complication have been greatly exaggerated. Pomeroy,⁶ Royston⁴ and others have already shown that a third-degree laceration of the perineum, when properly repaired, heals as readily as if the muscle were not torn. We share this opinion. Since using five-0 chromic catgut for repair, we have had ten cases of third-degree extension of midline incisions. There was no morbidity in any case and extended hospitalization was not necessary. Subsequent examination has shown adequate sphincter control with a well-supported perineum.

The use of the wooden tongue depressor for protection of the presenting part is simple and efficient. The resistance necessary for making the incision with adequate protection to the baby is well provided. Pressure from within aids in demarcating the structures to be incised.

A scalpel is used to incise the perineal body. Directing the knife-edge accurately in the midline insures cutting the fascia in the natural plane of cleavage. The additional space made available by incising the fascia of the transverse muscle bundle is considerable. The pressure of the presenting part forces the fascia edges laterally while the muscle stretches without tearing. The clean-cut edges facilitate closure. Because of the delicate caliber of the suture material, numerous sutures can be placed in a given area without fear of overcrowding with foreign material. The use of small needles (Murphy intestinal No. 4) encourages little additional trauma. Less pain results from the use of submucosal and subcutaneous sutures and permits early sealing of the incision, preventing contamination and reducing the pain. Bower, Burns and Mengle⁷ recently published their results with five-0 chromic catgut for gastrointestinal surgery. The reduction in tissue edema, ecchymosis, and local sloughing with

marked improvement in healing was well demonstrated. This corresponds to our findings over the past few years.

Over 300 patients treated by this method are available for study. The most notable improvement has been in the reduction of perineal pain following delivery. We attempted to obtain as reliable data as possible concerning perineal discomfort. However, subjective responses of patients do not lend themselves well to scientific analysis. We found only an occasional patient who experienced sufficient pain to require treatment. This discomfort was readily relieved by light therapy. All cases healed promptly. No morbidity attributable to episiotomy was evident. Post-partum examination has yielded gratifying results. The decrease in scar formation has been notable. Good perineal reconstruction has been the rule.

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DISCUSSION

DR. M. PIERCE RUCKER, RICHMOND, VA.—As much as I dislike the word routine, I do an episiotomy almost routinely in premature deliveries. I do it here for the baby's sake and in the full-term delivery for the mother's sake.

I have not used a knife and the wooden tongue depressor but am inclined to think that it is better than even a sharp pair of scissors. I have reduced the size of the catgut used to "0" and am glad to learn that smaller catgut is satisfactory. I use a continuous suture without knots as that is the only way I have been able to secure accurate apposition without constriction of the tissues when swelling and edema set in.

The only serious disagreement I have with the authors is the site of the incision. I like to keep away from the perianal skin as far as possible. Not only is it surgically dirty, but it is thin and hard to suture satisfactorily. The mediolateral incision gives more room, which is especially helpful when the patient has a funnel or male type pelvis. The disadvantages of the mediolateral episiotomy are more bleeding and possibly an asymmetrical closure. To overcome the bleeding I infiltrate the tissues with novocain and adrenalin. This has the advantage not only of making the procedure less bloody, but it permits one to stop the anesthetic when the head begins to crown. With this plan the babies are wider awake and the uterus has more tone during the third stage. No further anesthesia is needed for the repair. Asymmetry in repair is avoided by accurate anatomic apposition of tissues, and by observing such landmarks as the remains of the hymen, the mucocutaneous junctions and the pigmented skin.

DR. G. D. ROYSTON, St. Louis, Mo.—Midline episiotomy has the advantages of being easier to repair, giving a better anatomic result, and causing decidedly less discomfort. Yet I cannot view with equanimity the harmlessness of the third-degree tear. Among my first five midline episiotomies, two multiparas who delivered spontaneously suffered third-degree tears.

The midline incision has therefore certain limitations. These limitations are as follows: 1, any apparent disproportion, including a postmature baby or a child which seems to be unusually large; 2, faulty presentations; 3, contracted pelvic outlet where the narrow pubic arch forces the head backward, so that it must be accommodated at the expense of the posterior segment of the pelvic floor; 4, a low perineum, where the distance between the anus and vagina measures less than two inches. Since following these suggestions no third-degree tears have followed midline incisions in my hands.

DR. HODGKINSON (closing).—In looking over some 46 cases of third-degree laceration of the perineum that have occurred in the Henry Ford Hospital during the past several years, it was discovered that the bischial diameter was in the neighborhood of 9 cm. for most cases. This indicates that a contracted outlet is an important factor in the etiology of this laceration.

THE TREATMENT OF GONORRHEA IN THE FEMALE WITH SULFATHIAZOLE*

DUDLEY R. SMITH, M.D., AND ROGERS DEAKIN, M.D., ST. LOUIS, MO.
(From the Washington University Clinics, St. Louis, Missouri, in cooperation with the State Board of Health of Missouri)

THE recent improvement of results in the treatment of gonorrhea in women at Washington University Clinics is due to five factors:

1. The use of a safe and efficient chemical compound, sulfathiazole.
2. The use of improved methods of culturing the gonococcus on artificial media.
3. The development of improved technique in case finding and case holding.
4. The use of an adequate record form suitable for statistical analysis.
5. The education of the public about gonorrhea and its cure.

In a preliminary report,† we described our own examination and treatment record form for the individual patient. Since that time we have used and found satisfactory the record form recommended by the United States Public Health Service. A work or progress chart of the entire series of cases by weeks is desirable (Fig. 1). Examination of these charts reveals the progress of the individual patient and the clinic as a whole.

The experiences of one of us (R. D.) in the treatment of male gonorrhea since the introduction of the sulfonamides was the determining factor in our selection of sulfathiazole as the nearest ideal compound in eradicating the gonococcus in women. We have not regretted our selection of this drug.

*Read at the Fifty-Fourth Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

†J. Mich. State Med. Soc. 40: 440, 1941.

The newer methods of culturing the gonococcus in the laboratory are more efficient and simplified. The routine use of a culture from the cervix and the urethra will confirm the clinical diagnosis of gonorrhea; it will reveal the carrier and the occasional cases that are not diagnosed clinically. Adequate laboratory facilities were available to us for systematic bacteriologic study through the department of bacteriology of the Washington University Medical School.

TREATMENT OF GONORRHEA IN THE MALE FEMALE

March 1940

THERAPY— LOCAL:

ORAL: SULFATHIAZOLE (Gantrol) Four grains daily for five days

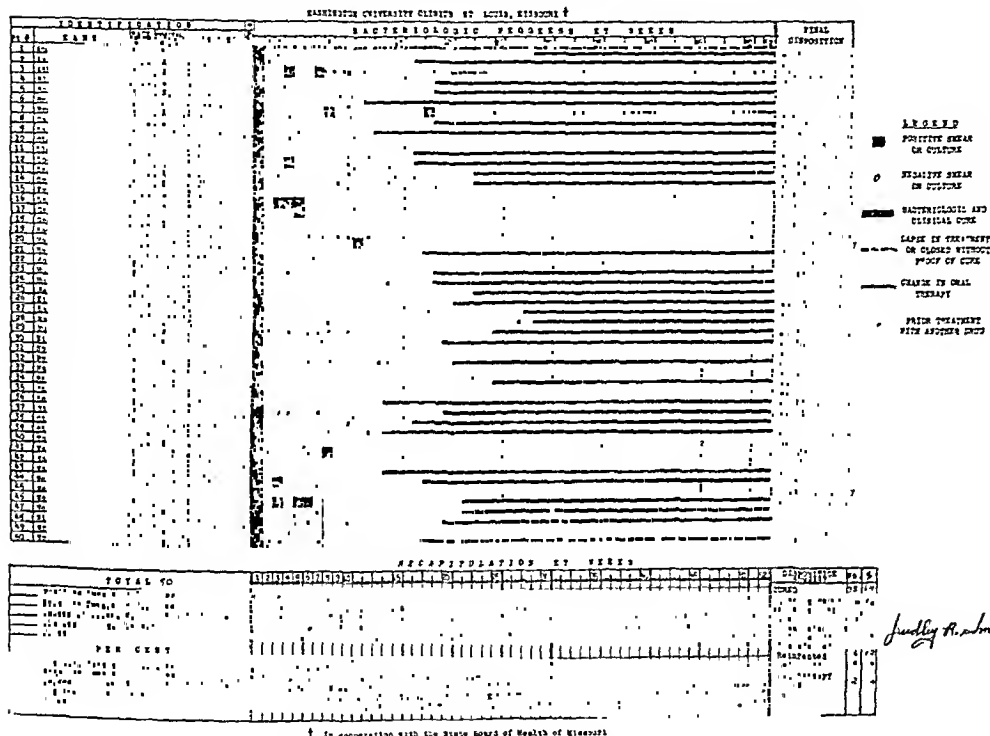


Fig. 1.—Sample progress chart of 50 cases.

METHOD

The material for a smear is taken from within the urethral canal by means of a platinum loop. A culture is taken from the urethral canal using a sterile cotton applicator. A bivalve speculum without lubrication is used to expose the cervix. A smear and culture are taken as from the urethra. A Gram stain of the smear is made immediately. The culture swabs are immersed in sterile broth until they can be plated on chocolate agar media.

Responsibility for case holding and case finding rests with a medical social worker who has charge of these activities in both male and female gonorrhea clinics. As a result of this joint supervision, a majority of the women under treatment are women named as the source of infection by patients in the associated male clinic.

The new patient is instructed by the physician concerning the nature of her infection, concerning the necessity for treatment, and in the precautions necessary to safeguard others. The patient is encouraged to ask questions about things not clear to her. Logical explanations are given in place of curt "Do's" and "Don't's." We find that time taken to improve education pays in better cooperation.

Each patient is interviewed by the social worker. He makes sure that the patient understands the treatment plan and medical instructions, he studies the social situation and searches for weaknesses that might cause the patient to lapse or interfere with treatment. He assists the patient to adjust herself if she is emotionally disturbed by the diagnosis of gonorrhea, obtains epidemiologic data, and builds up the patient's confidence and good will toward the physician and the clinic. Throughout, emphasis is placed on preventing lapses rather than pursuing the patient after she lapses.

The women in this group are mainly in the second and third decade. The women in our clinic are nearly equally divided between the white and the negro races. A few more are married than single. Eight were known to be pregnant at the time treatment was instituted. None admitted being professional prostitutes. They were all ambulatory patients. Each came for examination, treatment, and returned for observation of her own free will.

We take the usual gynecologic history, make a smear and culture from the urethra and the cervix and a bimanual palpation of the pelvis. The data obtained are recorded on the standard record form of the United States Public Health Service previously mentioned.

Our treatment routine has five divisions: chemotherapy, local therapy, focal therapy, fever therapy, and surgical therapy. Each is used when existing conditions justify such procedure.

Chemotherapy.—After a diagnosis is made, the patient is given sulfathiazole, 1 Gm. four times daily for five successive days. A smear and a culture from the urethra and the cervix have been taken at weekly intervals for three weeks, and at monthly intervals for three months; all six cultures had to be negative before the patient was discharged as cured. Recently the period of observation has been shortened to negative smears and cultures at weekly intervals for six weeks to conform with the recommendations of the Clinical Cooperative Group for Female Gonorrhea adopted at Cleveland in June, 1941. Due allowance is made to avoid examination during menstruation. A single course of the drug given to 110 women gave a cure in 71, a probable cure in 23, failure in 5, and 11 patients never returned. Two could not take the drug as directed because of nausea and vomiting. There were 7 of our patients who had a reappearance of gonococci that we were unable to differentiate, whether they were relapses or reinfections. Each patient was given a second course of sulfathiazole. They remained under observation until our criteria of cure were satisfied. In the group of 23 probable cures, 11 had three negative cultures, 5 had 4 negative cultures, and 7 had 5 negative cultures. If we disregard the probable cures and those that never returned, we have 71 known cures and 5

known failures; this is a cure per cent of 93.4. This result is very gratifying. There is some evidence that inadequate dosage and indiscriminate usage of the sulfonamides may lower the efficiency of sulfathiazole in rendering gonorrhea patients noninfectious.

If a positive culture reappeared before our criteria of cure had been satisfied, the infection was considered a relapse, and hence a drug failure unless there was definite evidence of re-exposure without prophylaxis to a known source of infection.

Local Therapy.—The recourse to local heat, enforced rest, adequate diet, and vaginal irrigations of 0.4 per cent lactic or acetic acid solutions has proved to be of value in acute and subacute infections resistant to chemotherapy. Perhaps the time element alone allowed these women to develop sufficient immunity to destroy their infections. Such a routine was demonstrated as worth while in two of our cases.

Focal Therapy.—Focal therapy is the next logical step in cases of persistent infection after failure of sulfathiazole and conservative local therapy. This includes destruction of the deep glandular tissue of the cervix, Bartholin's and Skene's glands. The popular conization and coagulating technique are effective in sterilizing the types of infection resistant to other forms of treatment. This was necessary in 4 of our cases. We have not yet had to repeat this procedure.

Fever Therapy.—The fourth step in our routine would be controlled sustained fever therapy. As has been previously pointed out by one of us (R. D.), this has been most effective in sterilizing stubborn types of infection resistant to chemotherapy and the accepted local and focal measures. Although it has not been necessary in this series, we suggest prompt utilization of fever therapy without recourse to local or focal therapy if chemotherapy has failed to stop a complicating arthritis or an ocular infection. We do not recommend fever therapy for acute salpingitis or pelvic cellulitis.

Surgical Therapy.—In spite of these improved forms of therapy, women will appear with abscesses of the lower abdomen and pelvis that require surgical drainage. Moreover, the previously outlined therapy will not relieve the semi-invalidism of the individual with a retroverted uterus and prolapsed adnexa bound down by extensive adhesions between the pelvic and abdominal viscera. Radical abdominal surgery is her only hope of relief.

SUMMARY

1. The coordinated effort of a clinician, bacteriologist and medical social worker will improve the management of gonorrhea in women in large clinics.

A joint male and female clinic aids materially in case control.

2. A comprehensive treatment routine is more effective than unplanned haphazard methods.

3. Group recording of results is desirable for statistical evaluation and for comparison of treatment procedures.

4. The use of specialized techniques by qualified personnel is essential to good case holding, case finding, and patient management.

5. Sulfathiazole is a safe and efficient chemical for the treatment of gonorrhea.

A single five-day 20 Gm. course of this drug has given us a cure percentage of 94.9.

Most of the sulfathiazole used in this study was furnished by the Department of Medical Research, Winthrop Chemical Company, New York, N. Y.

4952 MARYLAND AVENUE

607 NORTH GRAND BOULEVARD

DISCUSSION

DR. GRANDISON D. ROYSTON, ST. LOUIS, MO.—I have had the good fortune to observe the work reported by Dr. Smith and to study his careful methods of observation and follow-up work. Dr. Rogers Deakin of the Washington University Department of Urology is doing similar work with gonorrheal infected males, many of whom are consorts of the women treated by Dr. Smith. It is interesting to note that when an infected patient appears in the clinic of one of these men, his or her consort quickly and *voluntarily* appears in the clinic of the other.

Any ambulatory medical treatment for gonorrhea that cures within four to seven days about 94 per cent of those patients treated is a great advance. In cases resisting sulfathiazole, artificial fever therapy (106.6° F. for five hours) should be tried before resorting to any local or surgical procedures, however minor.

It has been found that at a temperature of 105.8° F. (41° C.), 99 per cent of gonococci are destroyed, in an exposure of four to five hours. The remaining 1 per cent of organisms require from eleven to twenty-three hours. This treatment can be exceeded in the human host without injury in the nonpregnant state. The average number of treatments is four, given every fourth day in a hospital with indications and contraindications similar to those for a major surgical procedure.

It must be recognized that tubal infection nearly always means some pelvic peritonitis and often troublesome adhesions. It must also be recognized that an associated cellulitis indicates a mixed infection. Sequelae resulting from these conditions may necessitate surgical intervention even after the eradication of gonorrheal infection.

DR. A. K. PAINE, BOSTON, MASS.—We have been using sulfathiazole at the New England Medical Center for eight months and our experience bears out what Dr. Smith has told us today. The procedure we carry out is that described by Dr. Cooke, namely a total dose of 20 Gm., 3 being given the first day and 2 the succeeding days. We had only two patients with a nausea and vomiting reaction. We made some blood studies and some observations of concentrations of sulfathiazole crystals in the urine but finally discarded both as unnecessary as routine procedures.

Excluding those of the last three months, we have treated 82 patients. Five of these we could not follow leaving 77 cases completely studied. No individuals were treated with sulfathiazole in whom a positive culture was not obtained. These patients have reported for smears and cultures after finishing the sulfathiazole at weekly intervals for one month, and then every two weeks for two months.

Seven of the 77 had positive smears subsequent to the course of treatment. The first one appeared in about two and one-half weeks, the last in three months after treatment. Whether these represent sulfathiazole failures or re-infections is very much a question in my mind. We will always have difficulty, of course, in these cases from the standpoint of reinfection.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—We have been carrying on a study very similar to this as a part of the work of the committee on gonorrhea in women of the United States Public Health Service. Among the more important things observed was the comparative worthlessness of the smear. Even with our excellent bacteriologic personnel we were unable to get a ratio of better than 1 positive smear to 2.9 positive cultures. We have, however, given up using urethral cultures, because we never got a positive one where there was a negative cervical culture. The best technique of making a culture we found to be the moving of the swab rather vigorously within the cervical canal. We obtained a higher number of positive cultures from direct spreads on the plates without previous broth culture.

As regards the sulfonamides, we had agreed with the committee to use sulfapyridine and are satisfied with it except for the fact that it frequently causes nausea. In such cases we have substituted sulfathiazole, with equally good results. We noted also that it takes longer to obtain a negative culture with sulfathiazole than with sulfapyridine; but there is a much lower incidence of nausea. Another fact about the sulfonamides was that only a small dosage is necessary. Our dosage is 3 Gm. the first day and 2 Gm. a day for nine days thereafter. We made daily cultures and found that with sulfapyridine we got a negative culture on about the third day, and with sulfathiazole on the fourth or fifth day. We have been taught that we should have rather high blood concentrations to obtain effective results, but with the dosage used, checked by a six months' follow-up, we got optimal results with low blood concentrations, frequently under 1 mg. per cent. Therefore, we did not have to subject the patients to potentially dangerous dosages.

We have, however, apparently established the fact of the sulfapyridine-fast organism. Many strains which responded well at first became sulfapyridine-fast subsequently. These cases apparently did not represent the introduction of a new strain of gonococci. We have not satisfied ourselves on the question of reinfection versus relighting of a latent infection. I do not think this can be determined without a study extending over a period of years.

We have now abandoned all local therapy. All of our patients with salpingitis are placed upon chemotherapy, with excellent results in the early cases. On the other hand, we found that the multiple recurrence cases with massive damage to the tube were definitely resistant to chemotherapy. This suggests that we were no longer dealing with a purely gonococcal infection, and that the damage to the tubes was wrought by some sulfonamide-resistant organism.

There has always been an idea that it is difficult to culture the gonococcus. We have not found this to be true. Using a freshly prepared proteose No. 3-hemoglobin-agar, and incubating in a CO₂ atmosphere created by permitting a candle to burn out in a closed can in which the plates were enclosed, we found this procedure very simple. The chief difficulty lies in the rapid deterioration of the culture medium. Mr. Charles E. Lankford, our bacteriologist, has found that by separately tubing the hemoglobin solution and proteose agar in 10 c.c. quantities, a plate may be poured or prepared at one's convenience by melting the agar, mixing the hemoglobin and pouring into sterile plates, thus eliminating this objection, the procedure becoming a very simple one for even the small laboratory.

Another thing we discovered was the relative unreliability of the average laboratory technician's report. We sent positive and negative slides to a number

of laboratories and had them give their technicians a practical examination on these slides. A totally unexpected number of both false negative and false positive reports were returned.

In this study we have cultured every patient going through the gynecologic and obstetric out-clinic. The frequency with which positive cultures are obtained from patients who showed no clinical stigmas of gonorrhea was astounding. In other words, there must be many individuals who are either carriers or have become immune to the gonococcus.

DR. SMITH (closing).—We selected focal therapy in preference to fever therapy in the women with the persistently positive culture from the urethra and the cervix for several reasons. One of these was that in our clinic at the University Dr. Melvin Roblee has been in charge of this work for many years, has used those treatments on well over 1,000 individuals and has not encountered a death. He has had less than 1 per cent morbidity and less than 1 per cent of the patients have had bleeding.

Many of you will agree with Dr. Royston, as I do for some cases, that fever therapy is preferable. For general clinic use, however, I do not believe that we can assist materially with fever therapy the work of the Public Health Service in eradicating infections in those women who would be likely to spread the disease. A very large percentage of those women belong to the lower strata of society that could not afford the treatment and probably would be very hard to manage. If the Public Health Service is correct in estimating some 250,000 new cases each year and if we assume that we are going to have at least a 5 or 6 per cent failure with sulfonamides, we will have some 15,000 individuals who will need further treatment. These would each have to have at least 4 fever treatments, perhaps as many as 6, making a minimum of 60,000 treatments. I do not believe our fever centers could handle them even if they were on the paying basis.

We take a smear as well as a culture at weekly intervals over a seven or eight weeks' observation period. We like to have two negative cultures following menstrual periods. The smear is of value to us, for a diagnosis is thus made immediately, not thirty-six or twenty-four hours later, and the treatment can be instituted at once. I have not used the immediate plating of the swab. Such a practice would possibly answer the problem raised when I have obtained positive smears, and the bacteriologist negative cultures. This combination occurs in only 10 per cent of patients. I believe in general that the continued practice of the clinician examining the smear and the bacteriologist the culture is the best.

✓ AN IMPROVED METHOD OF UTERINE CLOSURE IN HIGH CLASSICAL CESAREAN SECTION*

MILTON G. POTTER, M.D., AND NORMAN W. ELTON, M.D., BUFFALO, N. Y.
(From the Department of Obstetrics of the Millard Fillmore Hospital)

AFTER experience with some 3,500 high classical cesarean sections, we came to believe our prevailing method of suturing could be improved. An exhaustive study of the field impelled us to change our former technique in favor of a simplified method of uterine closure which more happily anticipates and precludes some of the retroactive effects of the prevailing method.

In common with other surgeons of our day, we recognize two methods of cesarean section: the low two-flap, so fashionable today; and the high classical method. This latter has come under considerable question because of the postoperative complications particularly in potentially infected cases and because of the prevalence of rupture. Avoidance of these complications in this operation was our problem.

There were many pitfalls for the surgeon in the latter procedure, wherein he placed three layers of sutures in a terraced manner, one above the other. This method gave the operator a false sense of security; so much so, indeed, that he was likely to ignore the fact that he was strangling tissue between his sutures which might be tied too tightly. If this proved to be the case, there was every chance that infarction of the muscle resulted, and this in turn would allow the lining of the uterus to invaginate into the sloughed-out area, thus weakening the scar.

These complications occurred too frequently to be ignored. It was natural, therefore, in our fortunate position of almost countless opportunities to observe the good and bad features of the, to us, only available method of procedure in cesarean section, for us to give much time and thought to a more effective plan. The result is that we have developed a technical method of closing the uterus which we know after 114 trials constitutes an improvement over the former closure in a high classical cesarean section.

METHOD

Following the incision and the removal of the baby and placenta, the fundus must be held firmly in the left hand of the operator, beneath and behind the incision. Clearly and easily by this means the endometrial border of the incision is exposed and thus the operator with his right hand is enabled to bevel off a portion of the endometrium. Closure of the incision by interrupted silk sutures, is then effected

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through the outer third of the uterine wall. To facilitate this closure the operator must retain his original grasp of the fundus (in his left hand) while using a long straight, round-pointed needle in his right hand. The sutures, which are spaced about one-fourth of an inch apart, are tied by the assistant, sufficiently tight to hold the parts intact without blanching of tissue. When this is completed, the uterus is dropped back into the lower abdomen. The abdominal cavity is not mopped out, the clots alone are removed, and the intestines, which have been protected by a rubber pad, are not handled. The abdominal incision is then closed in the usual manner with interrupted silk sutures.

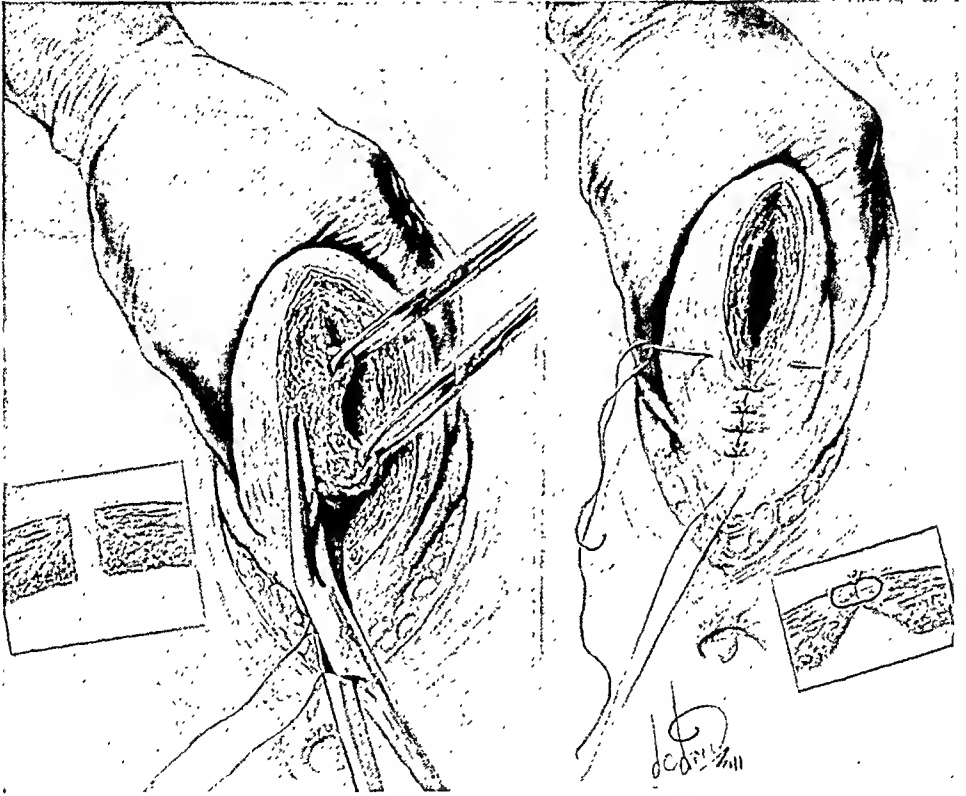


Fig. 1.

DISCUSSION

There have been many favorable factors governing our adoption of this new method. Out of 114 cases, we report 1 death, and in only 3 cases was there a morbidity of 100.4° F. on any two days excluding the first. In absentia are the specters that follow cesarean sections: post-operative nausea, vomiting, and abdominal distention. One of the outstanding clinical facts attending this method, is the marked absence of the usual postoperative bleeding, which was, in the three-layer technique a frequent occurrence. In only one case did we note excessive bleeding, which followed the removal of too much of the endometrial area.

Discussion of this problem reveals that some operators believe this method of closure marks too radical a departure, whereas others main-

tain that the under cutting of the lower border of the incision is unnecessary. The rationale of undercutting or beveling the inner surface of the wound, in addition to simple coaptation by a single row of interrupted sutures not placed deeper than the neutral level, is based upon our conception of defective uterine healing.

We believe that this mechanism of closure involves a play of stresses in the sutured incision above and below a neutral point in the uterine wall. This is characteristic of the mechanics of the shrinkage of a hollow sphere of soft tissue in which the resultant of the forces tends to produce, first, eversion of the wound through retraction of the outer layers, and, second, compression of the inner layers. As this sphere diminishes in size, thickening somewhat during the early phase of the process, the disproportion between the outer and inner layers is markedly accentuated. While the uterus is fully distended at term, there exists little difference between the outer and inner circumference of its mass, but as soon as contraction occurs after delivery, the inner circumference undergoes relatively much greater reduction than does the outer circumference. As a result, although the outer layers can adapt themselves readily to the available space, the inner layers are compressed and crowded into a rapidly diminishing and finally limited space inadequate to their bulk. Under these conditions the forces operating would tend to invert into the wall of the uterus, that portion of the inner layer which might be lying under a weakened part in the wall.

In addition to the stresses active at the site of the uterine incision during contraction after delivery, the damage to the myometrium by strangulating sutures comprises, in our opinion, the principal cause of defective healing following the three-layer technique of suturing. Segments of infarcted muscle may slough for several weeks after the operation, whereas others, remaining in place, undergo hyalinization. Infection, although secondary to tissue change, could occur in any of these wounds. Contamination of the wounds by endometrial implants seems unlikely, since there is small possibility of their survival in necrotic tissue.

The side walls of the wound may roll into the defect or not, depending on when the sloughs fall out. This rolling-in process, provided that sloughed infarcts have dropped out before involution is completed, is most prone to occur during the first days of the puerperium. Whether rolling-in of the endometrium occurs or not, sinus tracts of all shapes and sizes will develop, coming later to be lined by regenerating endometrium. Cross sections of these sinus tracts will appear as islands in prepared sections, but probing of the gross section almost invariably proves that they communicate with the general uterine cavity. Secondary sinus tracts may develop, and should the sinus involve the peritoneum, then the fistula tract, minute or extensive, of the ruptured uterus is created.

We have every reason to believe that our improved method of closure not only corrects the difficulties due to the stresses in the wall of the contracting uterus, but will also prevent strangulation of the muscle. In the presence of infection of any degree, this mode of suture permits free and adequate drainage into the uterine cavity, and it is equally adaptable to potentially septic cases as well as to clean electives. Hemorrhage is prevented by the natural physiologic forces of contraction and involution and should be no more encouraged to occur in the wound than in any other point in the uterus. If the sutures alone were responsible for control of hemorrhage, it is unlikely that the hundreds of venous sinuses exposed by the incision could be shut off effectively by any mode of suture without extreme strangulation of muscle.

This physiologic mode of suture has proved highly adaptable to many situations, including the complete excision of a defective scar in a previous cesarean section. Also, the removal of moderately sized fibroids along the line of the incision is made easy, and the risks of potential sepsis from mismanagement or tardy interference are minimized. Contraction is usually prompt and firm, except in the case when the internal os is obstructed by a segment of membrane; in this case, a clearance of the cervical canal produces the desired effect.

The accuracy in our reasoning regarding tissue healing has been reinforced by numerous observations on healed uterine tissues in other studies. The well-known tendency of the puerperal uterus to turn inside out when incised demonstrates the compressed-spring effect of the inner layers. The difficulty in coaptating the edges of the outer layers after they have been cut longitudinally or after the removal of fibroids provides additional illustration of this eversion tendency.

From our experience we know that suturing only of the outer layer after adequate undercutting of the lower border of the incision, as a part of the operation, must relieve the compression of the inner layers, facilitating contraction, controlling hemorrhage, and reducing the tension on the outer layers, while promoting better coaptation and healing during involution.

Looking down the long and painful road of the cesarean section case, historically speaking, it would seem that our findings in this improved uterine closure exemplify the rule that simple ways and means are best and safest.

DISCUSSION

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—No one can take exception to the fundamental mechanics of this idea. Incision into the active segment of the uterus during cesarean section always leaves the wound lying widely open on account of the greater retraction of the peripheral muscle layers. If the outer layers are brought together the first thing that happens is that the inner surfaces are jammed together, and the other parts of the uterine wall must of necessity lie contiguous to each other.

There are several questions that immediately arise. The first, hemorrhage is apparently of rather rare occurrence. From Dr. Potter's description, that risk is

more than offset by the elimination of the risk of sloughing due to the interruption of circulation. Second, we have an open wound in which there is no mechanical barrier to infection. Yet if infection does invade this open wound, drainage is immediate, and the defense mechanism is better able to take care of the infection than if drainage were interfered with by sutures. The principle is all right but the end results must be determined before the theory can be accepted as definitely proved.

When I read the paper I recalled an observation I once made on some cesarean scars. In two cases of uteri removed by hysterectomy some years after a most meticulous closure by a very expert obstetrician, the scars were terrifying. One exhibited multiple finger-like processes running out into the musculature, while the other was a simple bridge of scar tissue about the thickness of a postal card. Two of the other uteri that came into the laboratory were removed from patients who had been sectioned by a practitioner who never operated when even approximately sober. His method was to put in about three sutures almost anywhere, taking in almost any part of the uterine wall and in these uteri we were unable to find any trace of scar tissue by gross examination.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—The relation of wound reaction and lag in healing to the suture material used has interested me especially during the past ten years. Around catgut used in a wound closure there soon develops an intense polymorphonuclear infiltration within which and close to the catgut is a zone of tissue necrosis. Thus in a wound closed with catgut the early inflammatory and necrotic reaction so delays healing that the union is weakest about the seventh day and there is a tendency to suppuration.

Probably the operator who put only a few sutures in the cesarean wound reduced the reaction and thus had better healing, or perhaps he used silk instead of irritating catgut. In a septic field we have found nothing to equal nonirritating metallic sutures (ends cut very close to the knot) which are not extruded even under suppuration.

It would seem probable that weakness in a uterine wound may depend to a considerable degree on the basis of harmful reactions from the suture material, the reaction being increased by the large number or the large size of the sutures used.

DR. J. W. KENNEDY, PHILADELPHIA, PA.—The late Joseph Price and I have used interrupted through-and-through sutures of silk in the closure of all cesarean sections. There has not been a ruptured uterus following our work, and we have had but one postoperative complication in our experience. This consisted of a small sinus in the lower part of the abdominal incision, through which a few drops of blood would be extruded during each menstrual period.

In my early work I was timid in regard to inserting the suture in the uterine wall and was fearful that it would come in contact with the endometrium, but today our sutures of silk are used as through-and-through interrupted sutures. They are inserted less than 1 cm. apart and a greater amount of uterine structure is included on the peritoneal surface than that of the mucous membrane. This produces a V shape suture in its inclusion of uterine structure, so that there is less inclusion of the uterine wall near the endometrium than on the peritoneal surface. If this plan of suturing is followed, it will avoid the excessive pressure of the internal uterine wall to which Dr. Potter has called our attention.

I know of no location in all surgery where the anatomy of the part is so insulted as that seen in an attempt to divide the uterine wall into muscular and fascial planes, in order that the terrace method of suturing may be applied. It must be remembered that each buried suture is a ligature and has the potential dangers of crushing the tissues and is a foreign body in a dead space undrained.

We use through-and-through sutures of silkworm-gut in all our abdominal work, and there is no record of eventration of the viscera in the history of the institution. Absorbable sutures are never used.

DR. B. Z. CASHMAN, PITTSBURGH, PA.—I would like to ask Dr. Potter whether he has made any study of the scars with this new method of closure?

DR. POTTER (closing).—It was interesting to me in doing these cases and in our former cesarean sections to notice that most of the blood supply of the uterus is found in the outer one-third of the muscle, and it was our attempt in our interrupted sutures to catch those very large sinuses. The control of the hemorrhage which you may have noticed nearer the endometrium is done simply by the coaptation of the wall as the uterus involutes.

We are very pleased with our results with silk. We have been using silk altogether in the past several years, and we feel that it is an ideal drainage suture. We have not been doing this long enough to get specimens of our new scars, only recently I had the opportunity of doing a hysterectomy on a patient on whom I had done a cesarean section with this new method.

GONADOTROPIC HORMONE CONCENTRATION IN EMESIS GRAVIDARUM*

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(From the Department of Obstetrics, College of Medicine, Syracuse University)

SEVERAL years ago during the performance of routine diagnostic Friedman tests, it was noted that despite the use of a constant amount of urine, some reactions were much more intense than others. This was interpreted as meaning that some urine specimens contained more gonadotropic hormone than others. On investigation, it was found that most of the intense reactions were obtained with specimens from patients who were nauseated and were vomiting.

These observations suggested a possible connection between the nausea and vomiting of pregnancy and concentration of this hormone. It was decided to make a study along these lines.

A quantitative Friedman test was developed. We determined to find the least possible amounts of urine that would give positive Friedman reactions. It followed naturally that the smaller the amount of urine required to produce a positive reaction, the greater the concentration of hormone. It was felt that such a method might be more satisfactory to our purpose than attempting to isolate and assay the hormone.

Nonpregnant does weighing at least 1,500 Gm. and between sixteen and eighteen weeks of age were used. All animals were of the same or similar breed. Fractional intravenous injections of known pregnancy

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Aided by a grant from the Hendricks Research Fund.

urines were made in dilutions of 0.0125 c.c., 0.025 c.c., 0.05 c.c., 0.1 c.c., 0.5 c.c., 1.0 c.c., 3.0 c.c., etc. Two to six rabbits were employed for each test. The animals were laparotomized forty-eight hours after the injections. Corpora hemorrhagica or fresh corpora lutea were the criteria for a positive reaction.

A comparison was made of the minimum amounts of urine necessary to give positive reactions in the various weeks of early pregnancy. Four groups were compared, namely: Group 1, patients absolutely free from nausea or vomiting; Group 2, patients with some nausea and occasional vomiting, the so-called "physiologic vomiting of pregnancy"; Group 3, patients with excessive nausea and vomiting; and Group 4, definite pernicious vomiting of pregnancy. All the patients were observed personally and classified according to the above groups.

TABLE I

WEEKS	URINE (C.C.)			
	NO NAUSEA OR VOMITING	PHYSIOLOGIC NAUSEA AND VOMITING	EXCESSIVE NAUSEA AND VOMITING	PERNICIOUS VOMITING
5	1.8 (7)	0.5 (1)	0.5 (1)	
6	1.2 (8)	0.66 (3)	0.037 (2)	0.025 (1)
7	0.49 (11)	0.085 (7)	0.05 (1)	0.025 (3)
8	0.41 (5)	0.24 (8)	0.047 (3)	
9	0.50 (8)	0.16 (11)	0.121 (7)	0.018 (4)
10	0.35 (8)	0.23 (9)	0.047 (5)	0.019 (3)
11	0.5 (4)	0.45 (13)	0.04 (5)	0.027 (2)
12	0.45 (7)	0.39 (4)	0.05 (1)	0.025 (1)
13	0.83 (3)	0.5 (2)		
14	1.08 (6)	0.5 (2)		0.05 (1)
15	1.1 (5)	0.3 (2)		

The results of 173 quantitative urine tests are charted in Table I. Of these, 72 specimens were from patients with no nausea or vomiting; 62 in the group of physiologic vomiting; 24 excessive nausea and vomiting; and 15 pernicious vomiting. The number of tests for the various weeks of pregnancy is shown in the upper right hand corner of each box.

TABLE II

WEEKS	BLOOD SERUM (C.C.)			
	NO NAUSEA OR VOMITING	PHYSIOLOGIC NAUSEA AND VOMITING	EXCESSIVE NAUSEA AND VOMITING	PERNICIOUS VOMITING
5	0.5 (3)			
6	0.6 (5)	0.05 (1)	0.025 (1)	
7	0.27 (6)	0.045 (5)		0.025 (1)
8	0.10 (2)	0.062 (6)	0.05 (1)	
9	0.09 (5)	0.05 (7)	0.04 (5)	0.020 (3)
10	0.083 (9)	0.035 (5)	0.035 (5)	
11	0.075 (2)	0.122 (8)	0.037 (2)	0.05 (1)
12	0.1 (2)	0.05 (1)		
13	0.1 (2)	0.05 (1)		
14	0.42 (5)	0.5 (1)		
15	0.1 (2)	0.05 (1)		

The figures show the average amount of urine required to give positive reactions in cubic centimeters. A study of this chart shows that the greater the degree of nausea and vomiting, the smaller is the amount of urine required to produce positive reactions. Hence, it can be concluded that there is an increased concentration of gonadotropic hormone in the urine of patients with nausea and vomiting.

We have carried out a similar set of quantitative experiments on blood serum. Table II shows the results of 101 quantitative serum tests. The results are practically the same as with the urine determinations. There are a few exceptions, namely, in the ten-week group the average amounts

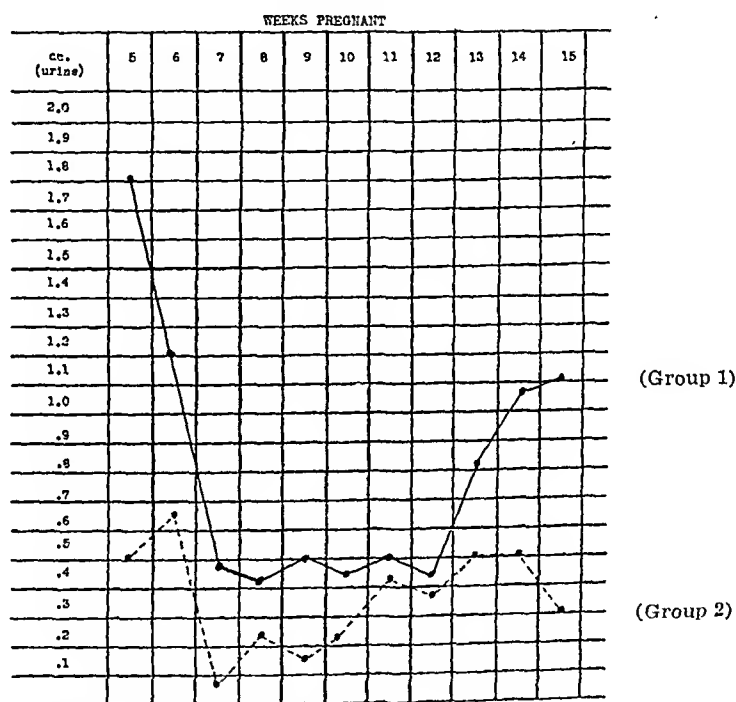


Fig. 1.—Chart showing fractional Friedman tests.

in Groups 2 and 3 are the same; in the eleven-week group, there is an average discrepancy between Groups 1 and 2; also in the fourteen-week group the average amounts in Groups 1 and 2 are approximately the same. However, in general it would seem fair to say that the serum studies confirm the findings of the studies on the urine specimens.

There is naturally one essential question that arises in this study. Is the increased concentration of gonadotropic hormone in the vomiting cases a true one, or is it simply the result of concentration due to dehydration resulting from the loss of fluids associated with the vomiting.

We are convinced from previous studies that simple concentration can be ruled out from the viewpoint of specific gravity determinations.

In order to further elucidate this particular phase, we have, in recent months, concentrated our studies on a comparison between Group 1, i.e.,

patients with no nausea or vomiting, and Group 2, i.e., physiologic nausea and vomiting. We feel quite certain from clinical observation of the latter group that there was not sufficient nausea and vomiting to upset the water balance. We believe, therefore, that the question of dehydration can be eliminated in a comparison of these two groups.

The findings of the urine studies (Fig. 1) demonstrate that less urine is required to produce positive reactions with the group of physiologic nausea and vomiting than is necessary in the group without these symptoms. This seems to justify the contention that simple concentration due to dehydration does not account for the findings.

DISCUSSION

We have presented evidence to show that there is an increased concentration of gonadotropic hormone in the urine of pregnant patients who present the symptoms of nausea and vomiting as compared to pregnant patients who are free from these symptoms. Similar evidence from studies with blood serum, in general, corroborates the urine studies.

One other observation seems pertinent. It is generally conceded that the greatest concentration of gonadotropic hormone is present from the sixth to the twelfth or thirteenth week of pregnancy. This is the same period of pregnancy during which clinical observation shows nausea and vomiting to be most commonly encountered. This relationship is probably significant.

The evidence presented is not necessarily conclusive that there is an etiologic relationship between increased gonadotropic hormone production and the nausea and vomiting of pregnancy. However, it is felt that sufficient data have been offered to allow speculation that there may be some relationship between a hormone disbalance and these commonly encountered symptoms. Certainly no satisfactory explanation has yet been presented to account for the early toxemias of pregnancy. We suggest, therefore, that the evidence presented may offer a possible explanation which future observations will prove or disprove.

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DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Schoeneck's work is of interest in its relation to the original investigations of Smith and Smith, which indicated a relative excess of chorionic hormone and a deficiency of estrogen in pregnancy toxemias. It appears, too, to indicate the role of the trophoblast in the production of gonadotropic principles, and might suggest the possible role of trophoblastic dysfunction, in the production of certain toxemias of pregnancy. Our knowledge is still too meager to draw any definite conclusions, and such efforts as have been made to apply these investigations therapeutically have thus far yielded rather disappointing results.

DR. ALBERT W. HOLMAN, PORTLAND, ORE.—I would like to suggest that in future work along this line the spinal fluid content be examined. In the reference to pernicious vomiting I believe the dilution was to 0.025 c.c. With hydatid mole the concentration of hormone is much higher and quantitative tests are positive in even lower dilutions. We know that in hydatid mole the spinal fluid content is positive, and I am wondering if in the serious cases of pernicious vomiting the spinal fluid estimation would be positive.

DR. SCHOENECK (closing).—Dr. Novak's remarks, of course, as to the practical application of these findings are very true. If our experiments are confirmed, however, it would seem that clinically we should administer large amounts of follicular hormone. This, of course, might be dangerous.

In reply to the remarks about the spinal fluid estimations, I suppose that can be done but I think it would be impractical with the method that we have evolved. I believe we could not get sufficient spinal fluid from the individual patient to make a practical test.

BLOOD TRANSFUSIONS IN PREGNANCY

A REVIEW OF 3,000 CASES

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UNTIL recently the dangers inherent in blood transfusions have not been emphasized. The early literature contains reports of a large number of reactions due to gross errors in typing, to failure to cross match, and to generally poor technique. As methods improved and the number of reactions decreased, more and more transfusions were given. The element of danger came to be disregarded. Recently, however, reports have appeared to suggest that severe reactions do occur even with improved technique.^{16, 27}

Within the last two years the dangers associated with transfusions have been brought to our personal attention by a number of incidents. Since all the severe reactions occurred in association with pregnancy, we suspected that it in some way predisposed to incompatibilities.

Even an incomplete review of the literature reveals a number of transfusion reactions in pregnancy in which no incompatibility was demonstrated by the routine methods.

Culbertson and Ratcliffe⁶ found two Group O patients with atypical agglutinins, both of which were in the puerperium. The authors call attention to the fact but attach no significance to it. Later, Levine and Stetson reported a case of intragroup agglutination and were the first to suggest that a mother could be immunized by a fetus carrying antigens inherited from the father.¹⁷ Jonsson¹³ found the average titer of Isohemolysins a and b to be higher than normal in women who had recently given birth. He attributes this finding to specific stimulation provided in cases of heterospecific pregnancy. For example, the presence of a Group A or B fetus in a Group O mother can produce a rise in the titer of Isoantibodies a and b, respectively.

Subgroups A₁ and A₂ and also A₁B and A₂B have been described and are known to cause mistakes leading to reactions⁸ but no fatalities have been attributed to these subgroups. And there are also other antigenic factors in the human blood which may cause reactions or the production of antibodies.

Of particular interest are the recent publications of Levine¹⁸ and Burnham⁵ in which the etiology of erythroblastosis fetalis has been established. They have called attention to the high incidence of severe transfusion accidents in mothers of erythroblastic babies. The Rh factor, present in the blood of the *Macacus rhesus* monkey and in 86 per cent of all human bloods of the white race, is inherited as a dominant property similar to the A and B factors of the four blood groups.

They have shown that an Rh negative woman carrying an Rh positive baby may, in certain cases, form anti-Rh agglutinins which pass

TABLE I

AUTHOR	AGE	CONDITION	BLOOD TYPES		PREM. CROSS-MATCHING	CHECK	AMT. GIVEN	TYPE OF REACTION	CONFIRMED AT AUTOPSY
			RECIP.	DONOR					
Culbertson and Ratcliffes	?	Dystocia, cesarean section	0	0	Compatible	Atypical agglutinins	?	Chill, temp. rise to 105° F. Anuria, N.P.N. up to 235 Mg. %. Recovered. Husband was the donor	
Daniels, Leonard, and Holtzman ⁷	28	Threatened abortion became incomplete	0	0	Compatible	Compatible	250 c.c.	Chill, moderate temperature rise. Uremia, died 8 da. after transfusion	Typical findings in the kidney
DeGowin ⁹ Case 8	25	Post-partum sepsis	AB	0	Donor's serum agglutinated patient's cells	Same	125 c.c.	Hemolytic react. without renal insufficiency. Feeling of constriction in chest. Patient lived	
DeGowin Case 10	26	Pyelitis of pregnancy	B	B	Compatible	Compatible	500 c.c. 500 c.c.	Second transfusion 19 days after first. Next day patient jaundiced. Second day delivered premature infant. Patient recovered	
Johnson and Conway ¹² Case 3	22	3 month pregnancy. Bleeding	?	?	Compatible	Compatible	500 c.c.	Hemolytic reaction. Died in uremia 18 days after transfusion	Focal areas of hemorrhage and necrosis in the liver. Typical kidney changes
Bordley ³ Case 7	36	Ruptured ectopic	0	0	?	?	?	Died in uremia on ninth day after transfusion	Liver: numerous areas of hemorrhage and necrosis mostly about the center of the lobule. Kidney: typical changes

Bordley ³ Case 8	32	Ruptured ectopic	A	A	Compatible	Compatible	?	No immediate reaction. Died in uremia on sixth day after trans- fusion	Liver: central necrosis. Kidneys: hematin in tubules
Bordley ³ Case 9	30	Ruptured ectopic	?	?	?	?	?	Died in uremia on eighth day after trans- fusion	
Bordley ³ Case 15	29	Anemia follow- ing pregnancy	A	A	Compatible	?	?	Blood urea to 354 Mg. %. Died in uremia on eleventh day after transfusion	Typical kidney change
Brines ⁴ Case 2	20	3 month preg- nancy. Vomit- ing. Thera- peutic abor- tion	0	0	Compatible	Compatible	500 c.c.	Gasped, became cya- notic and died 2 min- utes after transfu- sion. Husband was the donor	No explanation for the sudden death. Acute syphilitic myocarditis with coronary arteri- tis
Bancroft ¹¹	49	Incomplete abortion	Not given		Compatible	Compatible	400 c.c.	Chill lasting 20 min., temp. 103.4° F. Ann- rin for 9 days. Re- covered following de- capsulation of the kidneys	
Levine, Katzin, and Burn- ham ¹⁰ Pt. R. C.	32	Pregnant	0	0	Compatible	Atyp. agglu- tinins few days later	?	Patient went into uremia but recovered. Husband was the donor	
Pt. E. F. W.	38	Preeclampsia	0	0	Compatible	Same as above found on sixth day	?	Icterus, oliguria and Nitrogen retention— Recovered. Fetus had erythroblastosis fetalis. Husband was the donor	

TABLE I—CONT'D

AUTHOR	AGE	CONDITION	BLOOD TYPES		PRELIM. CROSS-MATCHING	CHECK	AMT. GIVEN	TYPE OF REACTION	CONFIRMED AT AUTOPSY
			RECIP.	DONOR					
Levine, Katzen and Burnham Pt. F. Z.	?	Placenta previa, cesarean, macerated fetus	?	?	Compatible	Type of agglutinins found just before death	?	Chill, fever, anuria, died in uremia 12 days after transfusion	
Pt. G. B.	32	Cesarean, fetal hydrops	A	A	Compatible	As above found on fourth day	?	Same as above, died on ninth posttransfusion day in uremia. Husband was the donor	
Pt. J. B.	30	Pregnant	?	?	Compatible	Compatible	?	Same as above, died on ninth day after transfusion in uremia	
Mandelbaum ²⁰	38	Pregnant B. P. 276/160	A	A	Compatible	Donor-A, Pt.-A ₂	500 c.c.	No chill or fever. Anuria, icterus, petechiae, and pruritus. N.P.N. went to 262 Mg. %. Patient recovered. Husband was the donor	
Bordley ³ Case 18	?	Ruptured ectopic	Given an auto transfusion				500 c.c.	Died in uremia 6 days after transfusion	
Parr and Kirchner ²¹	27	Menorrhagia, 6 wk. post-abor-tal	0	0	Compatible	Slow hemolysis of donor's cells in recipient's serum	400 c.c.	Vomited blood, hematuria, bled from needle wounds. Died four hours after transfusion. Husband was the donor	None reported

Goldring and Graefli Case 2	25	Abortion	0	0	?	Compatible Compatible Compatible	500 c.c. 360 c.c. 500 c.c.	7- 9-32 7-10-32 8- 6-32 (Husband) Following blood from husband, 4-plus albu- min, hematuria, N.P.N. to 180. Recov- ered	No autopsy
	24	Possible abor- tion	0	0	Compatible	Not done	400 c.c.	Died in uremia 14 days after transfusion	No autopsy
	24	Possible ectopic	0	0	Compatible	Compatible	500 c.c.	Chill, pain in back, anuria, and jaundice. Recovered	
Daniels, Leonard, and Holtzman	28	Long labor, high forceps retained pla- centa	0	0	Compatible	Not done	500 c.c.	No immediate one men- tioned. Hematuria, uremia, died 4 days after transfusion	Typical kidney changes, only congestion in the liver
Idem	43	Spontaneous abortion	B	B	Compatible	Right type after 20 min., Hemol. of donor's cells by patient's serum	500 c.c.	Palpitation, flush- ing, nausea, vomiting, chilliness and mild temperature rise. Oli- guria for 4 days N.P.N. up to 117 Mg. %. Patient recovered	
Idem	25	Incomplete abortion	?	?	Compatible Compatible	Not done Not done	500 c.c. 500 c.c.	Temperature rise. Se- vere chill, temperature to 105.6° F. Jaundice. Died in uremia on ninth day after sec- ond transfusion	No autopsy reported— second transfusion given 9 days after first. Time for anti- bodies to have devel- oped from the first transfusion
Idem	32	Abortion	A	0	Compatible	Not done	500 c.c.	As second above. Died 6 days after transfu- sion	None reported

back through the placenta to destroy the baby's blood. This Rh factor is thought to be responsible for about 90 per cent of all intragroup transfusion accidents after repeated transfusions or in pregnancy at the first transfusion.

It is also probable that the Rh factor causes many of the reactions between different groups that seem compatible by the Landsteiner method of cross-matching.

Furthermore, the pregnant woman and especially the toxemic one with her fatty liver, has poor protection against transfusion incompatibilities. In the case of hemolytic reactions the kidney of the pregnant woman, and especially of the toxemic one, is particularly vulnerable. The precipitation of hematin in already swollen tubules could quite possibly result in a fatal anuria, whereas an equal amount precipitated in a previously normal kidney might not be fatal.

A number of severe transfusion reactions have been collected from the literature. It is our opinion that scores of similar reactions have occurred unrecognized. Our own fatal cases were not recognized as such during life. The thought that others have had similar experiences is given credence by the report of a case at the Massachusetts General Hospital by Mallory.¹⁹ The patient (not pregnant) presented a picture which in retrospect was typical of a fatal blood transfusion reaction. Yet the pathologist's report of a blood transfusion death came as a complete surprise.

In Table I are collected 26 severe transfusion reactions occurring in pregnancy or the puerperium. Of this number, 16 died and 6 showed typical kidney changes. It will be seen that in 7 of the cases the reaction was caused by the husband's blood, even though in every case both parents belonged to the same blood group. Of special interest is the case of ruptured ectopic pregnancy reported by Bordley. This patient was given 500 c.c. of blood from her own abdominal cavity, and died in uremia six days later. In this instance one must consider the possibility that the patient had become sensitized to the fetus. This might occur in two ways. First, antigens in the fetal blood reaching the maternal circulation through a destroyed placental barrier could stimulate antibody formation in the mother. And second, absorption of antigens by the peritoneum could produce a similar result. It is doubtful if hemolyzed blood, otherwise compatible, would produce such a severe reaction. Tiber²⁴ mentions a similar instance. In 123 cases of autohemotransfusion there was 1 transfusion death. In 66 cases of ectopic pregnancy given both direct and autohemotransfusions, there were two transfusion deaths. In all instances rupture occurred more than seventy-two hours prior to transfusion. This incidence of transfusion deaths is extremely high.

The fact that re-cross-matching was not done in nine of the cases is an indication that a transfusion reaction was not thought of at the time.

On our obstetric and gynecologic services both minor and severe reactions came in such rapid succession that we became loath to order a

transfusion even when strongly indicated. In other departments, transfusions were given with relative impunity. A survey was consequently made of 3,000 transfusions given in the last three and one-half years in the St. Mary's Group Hospitals of St. Louis. Our findings are given in Tables II to IV.

TABLE II. SHOWING GREATLY INCREASED INCIDENCE OF TRANSFUSION REACTIONS AMONG THOSE GIVEN TO PREGNANT PATIENTS OVER THOSE GIVEN TO NONPREGNANT ONES

	NUMBER OF TRANSFUSIONS	NUMBER OF REACTIONS	PER CENT OF REACTIONS
To nonobstetric cases	2,604	299	11.4
To obstetric cases	396	82	20.9
To all cases	3,000	381	12.7

TABLE III. INDICATING INCREASED INCIDENCE OF TRANSFUSION REACTIONS AMONG PREGNANT PATIENTS

	NUMBER OF PATIENTS	NUMBER REACTED	PER CENT REACTED
Nonobstetric cases	1,108	215	19.4
Obstetric cases	151	61	40.6
All cases	1,259	276	22.0

TABLE IV. SHOWING INCIDENCE OF TRANSFUSION REACTIONS WHEN THE HUSBAND WAS THE DONOR AS COMPARED TO OTHER DONORS. IN OUR SERIES THERE IS NO SIGNIFICANT DIFFERENCE

	NUMBER OF TIMES	NUMBER OF REACTIONS	PER CENT OF REACTIONS
Husband donor	40	9	22.5
Other donors	356	73	20.5

In the entire series 313 bank blood transfusions were given with 57 (18.2 per cent) reactions. The balance was citrate transfusions with 324 (12.7 per cent) reactions. As here enumerated, reactions consist of urticaria, or a chill and at least a 1° (F.) rise in temperature. Urticarial reactions alone were evident in 50 out of 381 reactions.

CASE HISTORIES

CASE 1.—Patient, D. K. (No. 40-1257), aged 24, para i, gravida ii, entered the hospital in labor with a blood pressure of 145/102 mm. Hg; she delivered a one-month, premature living baby after a twelve-hour labor. There was minimal blood loss but patient went into shock. The patient, Type A, was given 1,000 c.c.* of bank blood from an O donor. An hour after the transfusion started the patient had a chilly sensation and nausea, with temperature rise to 102.8° F. axillary two hours after the transfusion. The patient failed to respond and another transfusion (donor Type A) was given with no reaction. During the next forty-eight hours, the blood pressure remained between 66/32 and 94/70. There followed decreased urinary output during the next six days, the nonprotein nitrogen rising to 83 mg. per cent on the fourth day. On the second day ieterus index was 26. The red blood count dropped from 3,930,000 immediately after the second transfusion, to

*One thousand cubic centimeters of bank blood contains 400 c.c. of blood and 600 c.c. of dextrose citrate solution.

2,730,000 four days later. The urine contained 1- to 3-plus albumin and microscopic blood up to the fifth post-partum day. Patient recovered and returned home on the twenty-sixth post-partum day. Cross-matching was not repeated.

CASE 2.—Patient N. V. (No. 39-18029), aged 29 years, para i, gravida ii, entered the hospital two weeks before term with vaginal bleeding that was found to be due to partial placental separation. Patient, Type B, was given 400 c.c. of citrated blood from a B donor. Ten days later 1,000 c.c. of bank blood were given from a B donor, followed by a chill, temperature rise from normal to 103° F., drop in blood pressure from 90/60 to 60/40, emesis of bright red blood, and fetal heart tones, which had been present before the transfusion, could no longer be heard. A diagnosis of premature separation of the placenta was made and confirmed at a cesarean section done under local anesthesia. A dead child was delivered. The mother died on the eighth postoperative day of a *B. welchii* bacteriemia. But the nonprotein nitrogen steadily rose to 120 mg. per cent two days before death, the urine contained occult blood and two-plus albumin and with decreased urinary output. In addition to her infection this patient undoubtedly had a severe transfusion reaction which, of itself, may or may not have otherwise caused death. There was no autopsy, and no re-cross-matching.

CASE 3.—Patient C. D. (No. 40-468), aged 26 years, entered the hospital two weeks past term. The patient, Type AB, after a thirty-six-hour labor was delivered of a 9½ pound living baby by cesarean section. Before the patient roused from the operation she was given 1,000 c.c. of bank blood, Type O, and no immediate reaction was noted. Four hours later the temperature was 103° F. The urinary output was diminished and the nonprotein nitrogen rose to 150 mg. per cent the day before death, which came on the eighth postoperative day. The urine contained two plus albumin, 15 to 20 red blood cells per high power field and granular casts.

Essential Pathologic Findings.—Gross: Liver: Weight 1,750 Gm. Liver showed on cut section focal areas of hemorrhage and congestion in the area of the central vein. Kidneys: Each weighed 200 Gm. There was evidence of swelling, no evidence of infarction; cortex, calices and pyramids showed no abnormalities. Microscopic: Liver: Focal areas of congestion, degeneration, atrophy and necrosis of the liver cell cords that appeared quite constantly about the central vein (see Fig. 1). Kidney: Most of the glomeruli showed little morphologic change, though the tuft was frequently shrunken, and Bowman's spaces contained amorphous material in round pale bodies suggestive of hemolyzed red blood cells. The epithelium of the convoluted tubules showed a mild degenerative (nephrotic) change. In the medulla, the collecting tubules were almost all filled by amorphous, granular or hyaline material. In some, red blood cells were present (Fig. 2).

CASE 4.—Patient M. S. (No. 40-4559), Type O, aged 35 years, para i, gravida ii, entered the hospital about the thirtieth week for a cesarean section because of a blood pressure of 180/105 mm. Hg and an extensive retinal hemorrhage. The first pregnancy had been complicated by hypertension of 180/100, two-plus urinary albumin and a section for primary uterine inertia. Immediately after the second cesarean section she was given 500 c.c. of citrated Type O blood which was

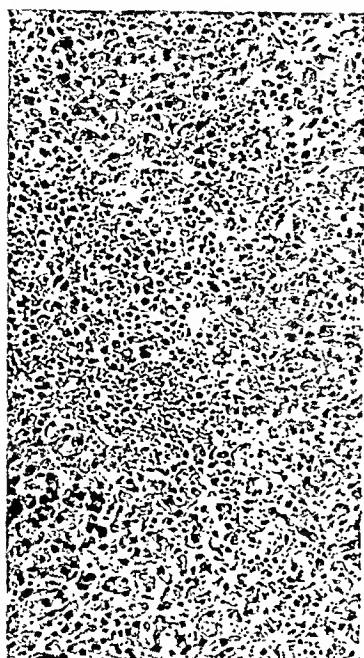


Fig. 1.



Fig. 2.



Fig. 3.

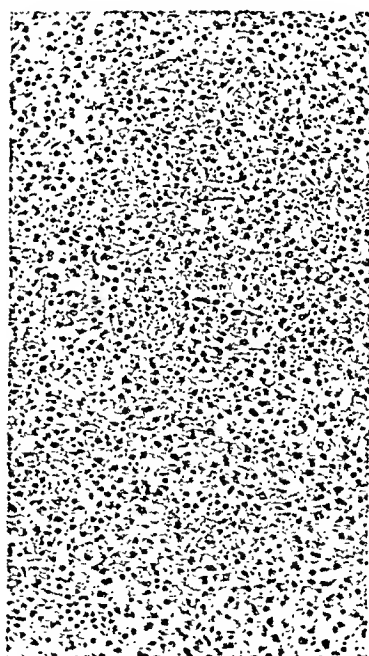


Fig. 4.

Fig. 1.—Case 3. Liver, showing focal areas of congestion, degeneration, atrophy and necrosis about the central vein. ($\times 140$.)

Fig. 2.—Case 3. Kidney, hemolyzed red blood cells in the convoluted tubules. ($\times 140$.)

Fig. 3.—Case 4. Kidney, hemoglobin casts in the kidney tubules. ($\times 140$.)

Fig. 4.—Case 4. Liver. Thickening and swelling of liver cord cells, no areas of necrosis. ($\times 140$.)

followed by a chill and a temperature of 101.6° F. On the following day the patient was given 500 c.c. of citrated blood from a Type O donor with no reaction. Because the patient failed to get the usual benefit from the preceding transfusion, another 500 c.c. of citrated, Type O, blood were given five days later, and were followed by a chill and a rise in temperature up to 101.2° (rectal) from normal. Three days later 250 c.c. of citrated Type O blood were given and repeated the following day, both without reaction. The patient gradually became jaundiced, the red blood count and hemoglobin fell in spite of the transfusions, and the nonprotein nitrogen rose to 200 mg. per cent when the patient died on the eleventh postoperative day. Urine showed albumin 2- to 3-plus, red blood cells, and hyaline and granular casts. There was the usual depression of fluid output which was returning just before death.

Pathologic Report.—*Gross:* Liver: Normal size, firm in consistency, smooth, and on cut section showed a yellow homogenous appearance. Kidneys: Approximately two times normal size. Weight of both 500 Gm. Capsule stripped easily and displayed smooth surface, mottled in appearance. On cut section these mottled areas could be seen in the cortex. *Microscopic:* Kidney: H and E stains showed marked tubular degeneration. There was marked granularity and swelling of the cells of the proximal convoluted tubules, with hemoglobin casts found in both in the convoluted tubules and tubules elsewhere (Fig. 3). Liver: There were no well-defined areas of engorgement or thrombosis of the sinusoids, and there were no definite areas of liver cell necrosis (see Fig. 4).

DISCUSSION

It has been our experience that transfusion reactions are common in pregnancy and the puerperium. A number of cases from the literature are presented which are similar to ours. It is our opinion that a careful study of all transfusions in pregnancy will reveal a great number of reactions hitherto attributed to some other cause.

In none of our fatal cases was a transfusion reaction recognized before death. This is unfortunate because valuable determinations remained undone. One of our fatal cases (C. D.) was transfused before she had been roused from the operation and no chill was observed. In two of the others, the immediate reaction was not more severe than any number of ordinary transfusion reactions without serious sequelae. This fact often is responsible for failure of physicians to recognize that the patient has received incompatible blood.

In our series of 3,000 transfusions, the percentage of reactions, both mild and severe, was higher in the pregnant patients. Since all these transfusions were administered under similar conditions, it would appear that pregnancy presents certain phenomena which make it more difficult to transfuse safely. Among these phenomena, the following should be considered:

1. Anemias of pregnancy or those resulting from abortions may lead to errors of grouping through "pseudo-agglutination."²² The strain on an anemic myocardium due to a severe rigor superimposed upon an increased blood volume may result in a fatality.

2. Infections, as seen in puerperal sepsis, have long been known to carry a high percentage of reactions.

3. Patients with kidney damage, both glomerular and tubular, also have a high percentage of reactions. This applies to the toxemias of pregnancy.

4. Atypical agglutinins have recently been shown to cause severe or even fatal reactions. It has also been shown that in pregnancy the proportion of patients with these agglutinins is unusually high.

One or more of these factors may be present in a given case. Only by early recognition of the reaction can the cause of the incompatibility be determined. An investigation in a suspected case of incompatibility should include the following tests:

1. Re-cross-matching of the original blood samples, using the method of Levine.¹⁸

2. Re-cross-matching following the reaction. If no incompatibility is found, it may be that the agglutinin is absorbed by the donor's blood. Or an agglutigen may be absorbed by the recipient's blood. A re-check in four days or more will reveal the error.

3. Determine if the Rh factor or subgroups of A or AB are responsible, if this is possible.

4. Careful check of apparatus, methods of collecting and administration, and titers of test sera.

5. Daily examination of the urine for microscopic and occult blood. Icterus index, serum bilirubin and Hb determinations, accurate fluid summary, and frequent temperature and blood pressure readings.

Certain implications are apparent from the foregoing. The indiscriminate giving of blood in pregnancy is deprecated. We hasten to add that we do not condemn the use of transfusions in pregnancy. We recognize it as one of our most valuable therapeutic weapons. Occasions arise where the urgency for blood is so great that atypical reactions cannot be considered. But oftentimes in cases of mild shock with moderate blood loss, in the toxemias of pregnancy, and postoperatively, intravenous glucose or plasma may serve the same purpose with less danger. In any case where time permits, every precaution should be taken to detect incompatibilities. The usual cross-matching should be replaced by the centrifuge method of Levine,¹⁸ in which the patient's serum and donor's cell suspension are incubated for thirty minutes at 37° C. and then centrifuged at low speed (500 r.p.m.) for one minute and read as in the usual Landsteiner method. The laboratory should be notified that the patient is a "pregnancy case" and should take special care in the selection of donors. The alkalization of the urine to prevent the precipitation of acid hematin in the kidney tubules has been found helpful and should be used. In the toxemias, potassium bicarbonate is suggested.

The phenomenon of sensitization of the mother to the fetus brings out some interesting speculations that may be of greatest importance and which require further investigation.

In his book on *Abortion*, Taussig²³ states that a tendency to abortions has been observed where there was a difference in the blood groups of

husband and wife. Levine, Katzin, and Burnham¹⁶ in their discussion on the possible bearing of iso-immunization on the etiology of erythroblastosis fetalis, mention habitual abortions and premature death of the fetus in several instances.

As long ago as 1905, Dienst¹⁰ touched on this phenomenon as a possible cause of eclampsia. It is known that a woman, carrying a fetus which has inherited certain antigens from the father which are absent in herself, may become sensitized to her child. Chorionic villi with patent capillaries have been found in the maternal circulation. It is therefore not difficult to conceive of a series of blood transfusions in miniature in which small amounts of fetal blood enter the maternal circulation. Levine and his associates indicate that antigens and antibodies may pass through the intact placenta. As the titer of antibodies in the mother rises, the reaction to fetal blood or fetal antigen increases. The similarity of the liver and kidney pathology in eclampsia and in transfusion deaths is striking. The former may be considered a chronic condition, the latter an acute episode. Further investigation will determine whether repeated small transfusions of incompatible blood will cause thickening of the glomerular basement membrane, which is the one distinguishing renal lesion in eclampsia.²

CONCLUSIONS

1. The pregnant or puerperal woman is more susceptible to all types of transfusion reactions.

2. In a series of 3,000 transfusions there were 12.7 per cent reactions. In 396 transfusions given to obstetric patients, there were 20.9 per cent reactions, whereas there were reactions in only 11.4 per cent of the non-pregnant cases. Of all the obstetric patients transfused, 40.6 per cent had reactions, while only 19.4 per cent of the nonpregnant patients reacted.

3. From the material found in the literature, we feel that it is probably safer not to use the husband as a donor without special compatibility tests. However, in our series the increased incidence of reactions was not significant.

4. Four severe transfusion reactions are reported. All occurred in association with pregnancy, and there were two deaths with autopsy.

5. Except in emergencies, the selection of donors should be made with special care and the patient prepared for transfusion by alkalization.

6. A procedure is suggested for investigating suspected cases of transfusion reaction.

7. The phenomena underlying the increased incidence of transfusion reactions in pregnancy have been shown to cause erythroblastosis fetalis and may produce certain toxemias of pregnancy.

We wish to thank Dr. William C. Stude for the use of one of these cases and Dr. Grey Jones for the use of a case and for his helpful suggestions. We also wish to thank the Department of Pathology for their cooperation in this work.

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4500 OLIVE STREET

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The author reviews the literature on pregnancy in the abnormally formed uterus and presents a detailed study of 19 such cases. He finds that exclusive of unfavorable position, poor contractions, and early separation of placenta there may be expected with great regularity many unusual conditions affecting the fetus, such as amputations and developmental defects as well as all possible malformations of the placenta. The peculiarities of placentation are attributed to faulty implantation. Hyperemesis or pre-eclampsia often occurs. The increased incidence of toxie conditions in association with uterine anomalies is attributed to a more or less generalized constitutional weakness of the pregnant woman.

R. J. WEISSMAN.

POSTOPERATIVE HORMONAL THERAPY TO SPARE REMAINING OVARIAN TISSUE*

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IT HAS always been, and still is, my practice to treat ovarian tissue in a conservative manner when possible. There has never been, however, any hesitation at sacrificing an ovary, the adequacy of whose blood supply I questioned in the least.

In 1932 I realized with concern and dismay that in an appreciable and increasing number of young women it had been necessary for me to remove their remaining ovarian tissue. Since that time, accurate records have been kept of all such cases that came under my care. Included in each record is a follow-up for not less than six months in all cases and for years in many cases.

During the year 1932 pathology was encountered in 7 women which required excision of one ovary with or without some procedure, such as resection, enucleation of a single cyst or puncture of multiple cysts on the other ovary. Subsequently 3, or 40 per cent, of these women required, because of acute and incapacitating pain, removal of all remaining ovarian tissue at a second operation. In each instance, at the first operation, one ovary had been excised and the other resected and sutured with plain catgut. Within that same year 6 women who had been operated upon by others, lost, in my hands, their remaining ovarian tissue. The record in each of these cases was obtained and carefully studied. In all of them, one ovary had been removed and the other ovary had, no procedure in 1 case, puncture for multiple cysts in 1, enucleation of a single cyst in 1, and resection and continuous suture with catgut in 3.

The procedure applied to the ovarian tissue allowed to remain at the first operation must have been faulty, not only in my hands but in the hands of others. Since in all 3 of my cases and in 3, or one-half, of the others, the resected ovary had been sutured with catgut, it was decided to abandon that procedure in favor of enucleation or multiple puncture whenever possible. When necessary to resect, bleeding points would be tied individually.

In 1933, of 9 women from whom one ovary was removed, some procedure was necessary upon the other ovary in only 7. But subsequently of these 9 women 3 required a second operation for removal of remaining ovarian tissue. In 1 of them nothing had been done to the second ovary while of the others 1 had been subjected only to multiple puncture and 1 had been resected and individual bleeders tied with catgut. During this year, it was necessary to remove remaining ovarian tissue from 8 women

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whose initial operation had been done by others. In all of these one ovary had been removed and the other had, no procedure in 2 cases, multiple puncture in 3, and resection with continuous suture in 3.

There still seemed to be some fault in the technique. It was decided to try a careful decortication with control of bleeding by pressure from hot packs and only to resort to any other procedure when absolutely necessary.

In 1934, of 10 women who lost one ovary, the above procedure was done upon the other ovary in 7 instances, no procedure in 2, and resection with individual ties in 1. Of these 10 cases, 3 came to subsequent removal of remaining ovarian tissue: at first operation 1 had no procedure, while 2 had been decorticated. During this year remaining ovarian tissue was removed from 6 women whose first operation had been done by others. In 1 of these, both ovaries had been resected and continuously sutured, while in the other 5, one ovary had been removed, and the others had, no procedure in 2 cases, multiple puncture in 1, and resection with continuous suture in 2.

Changing of technique had resulted in only a 10 per cent decrease of an altogether too high percentage of patients requiring removal of remaining ovarian tissue. In 9 of 26, or 35 per cent, of my cases and in 20 cases of others this had been necessary. In 7, or 25 per cent, of these 29 cases, nothing had been done to the second ovary and in the 2 cases in my series certainly, and presumably in the other 5 cases also, the blood supply to the ovary had not been knowingly interfered with. Careful study of the history of these 29 cases, all between 19 and 36 years, revealed the following interesting facts:

1. In all cases symptoms of increasing-in-size masses, ranging from local discomfort and a sense of heaviness to a dull ache to actual pain, first appeared in from four weeks to not longer than five months after their first operation, and became severe enough to require operative relief.

2. In none were noted symptoms of hypo-ovarianism.
3. In 20, or 70 per cent, menstruation was as regular as formerly.
4. In 6, or 20 per cent, menstruation was more frequent.
5. In 3, or 10 per cent, menstruation was less frequent.
6. In 17, or 60 per cent, amount or length of flow was unchanged.
7. In 7, or 25 per cent, amount or length of flow was increased.
8. In 5, or 15 per cent, amount or length of flow was decreased.
9. In 3, or 10 per cent, dysmenorrhea was greater than formerly.
10. In 12, or 40 per cent, there was hemorrhage, old or recent, into a simple cyst while 17, or 60 per cent, were simple serous cysts.

It seemed remarkable that these cysts should cause actual pain since simple cysts are not usually painful. Here it is well to recall that all patients developed pain in not more than five months. This rapidity of development, perhaps, accounts for the pain. It also seemed fairly evident that the development of these cysts was not due entirely to scarring of the cortex. It appeared distinctly worthy of note that, although

these cysts developed rapidly, there was little or no suggestion of a deficit of, or interference with, ovarian hormone. It, therefore, was reasonable to assume that the remaining ovarian tissue had taken over all ovarian hormonal duties. It might be argued that these duties had been gradually shifted since one ovary presumably had been fairly slow coming to be of so little value that its removal was indicated. This, however, is not histologically so, because it is a rare ovary that has not some useful areas in it. The sudden operative elimination of even small functioning areas would, thus, cause an immediate burden to be placed upon remaining ovarian tissue. It occurred to me that we might ease down or "spare" this sudden call for an all-out effort on the part of depreciated ovarian tissue by giving a supply of hormone in the form of estrogenic substance. It was and is conceded generally that increased work of a human organ requires greater blood supply than normally. Cyst formation in an ovary whose blood supply has been interfered with is well known and is seen all too often following a salpingectomy. That estrogenic substance might not only supply additional hormone but might also cause increased blood supply to remaining ovarian tissue was hoped on the basis of 2 then recently observed cases. Both of these women had been operated upon elsewhere years previously, losing all of one ovary and a part of the other. Several years had passed for each of them before menopausal symptoms appeared. When menopausal symptoms appeared, they were so severe that it had taken huge doses of estrogenic substance to relieve them, one patient having been given 48,000 units in one week and the other 60,000 units in eight days. Pain, rapidly increasing, and a very tender cystic mass in the pelvis caused me to operate. In each patient was found an ovarian cyst distended with fresh hemorrhage.

Believing that moderate doses of estrogenic substance could, at the very least, do no harm, it was decided that each patient who lost a considerable part of her ovarian tissue should be given estrogenic substance according to the following program: 2,000 units of estrogenic substance in oil to be given intramuscularly at a single dose each week when not menstruating; first dose eight days after operation; postmenstrual dose five days after cessation of flow. Because, in the 29 cases studied, symptoms began invariably within the first five postoperative months this program was to be continued for six months postoperatively. Each patient falling into this group has had a minimum of postoperative pelvic examination at about six weeks, about three months, about six months, and about every six months thereafter when feasible. Those in whom any pathology was found were examined more frequently, immediately premenstrually, immediately postmenstrually, and intermenstrually.

This report includes all cases from January, 1935, through December, 1940, with follow-ups through June, 1941, a total of 57 women, varying in age from 18 to 34 years, whose pathology required removal of a part of their ovarian tissue. To state it in other words, all these 57 women retained part, but not all of their ovarian tissue. When the blood supply

to an ovary was questionable that ovary was removed. Procedures followed upon remaining ovarian tissue were: 44 decortications, 7 enucleations of single cysts, 5 multiple punctures, 18 resections with interrupted suture or with individual ties of bleeding points; a total of 74 procedures in 57 patients. This discrepancy is accounted for by the fact that, in 17 instances, only a part of both ovaries was removed but that part always equalled at least half of the ovarian tissue.

In only 2, or $3\frac{1}{2}$ per cent, of these 57 women was postoperative pathology found. Neither of them has required operation. In a 19-year-old girl with pelvic inflammatory disease, somewhat more than one-half of each ovary was resected and bleeders tied individually; both tubes and appendix were also removed. Twenty-nine days postoperatively, at what proved to be three days premenstrually, she complained of pain in the left lower quadrant of the abdomen radiating to the back and rectum. This pain was described as a severe ache, continuous and without nausea. Pelvic examination the same day disclosed only a tender mass, 4 cm. in diameter, lying quite low in the left adnexal region but not in the cul-de-sac. She had received 3 doses of 2,000 units of estrogenic substance; the next dose was due the same day and was given. This patient has been carefully watched during the ensuing four years and in June, 1941, the mass was no larger and she has been symptom-free for more than three years. Menstrual periods have occurred regularly at twenty-eight-day intervals and have been painless and unremarkable. Estrogenic substance was given to her according to schedule until all pain ceased, at the end of eight months, when it was discontinued. Perhaps larger amounts immediately postoperatively might have prevented the formation of this cyst. The other case was a 31-year-old woman from whom one multiple cystic ovary was removed three years ago, at the time of a total hysterectomy; the other ovary which was sclerocystic was decorticated. Three months postoperatively she complained of a heaviness and aching in the right side of the pelvis. She had received estrogenic substance as planned. At examination only a tender mass, about 5 cm. in diameter, was found in the right side of the pelvis. Her pain ceased after seven months during which time she received estrogenic substance routinely. She still has a cystic mass, perhaps slightly smaller than originally, but remains entirely free from pain.

During this six-year-period 47 women from whom others had removed part of their ovarian tissue have been seen. Of these, only 28, or 60 per cent, required removal of their remaining ovarian tissue. The other 19, or 40 per cent, presented themselves early upon the development of postoperative discomfort or pain and were treated with estrogenic substance according to our routine except that in 6 cases the first 4 doses were of 10,000 units weekly. They have been carefully followed. Increase in size of mass ceased almost at once while pain and discomfort ceased in never longer than nine months. None of these 47 women had received estrogenic substance before consulting me.

DISCUSSION

Greenhill¹ states that "Conservative surgery of the ovaries should be reserved for only a certain proportion of women under 40 years of age." When he states, "In young women it is far better to risk the necessity of another operation a few years later" he implies that such

necessity is not infrequent. He² again states, “. . . . an ovary should not be removed unless it is absolutely necessary, especially in a young woman. One can never tell when the remaining ovary may have to be removed” Runge³ found a 15.5 per cent incidence of cystic ovaries in 196 traced women of 345 from whom one ovary had been removed. If the remaining ovary was subjected to no procedure, and no mention is made of such procedure, his figure is lower than my 25 per cent in 29 cases, but still high. Other statistics of the incidence of cyst formation in remaining ovarian tissue have not been found.

The incidence of 35 per cent in my present series of 26 cases, 1932 through 1934, under various types of operative technique, may seem high but, perhaps, other analyses might find it just as high or even higher.

SUMMARY

1. From 1932 through 1934 varied operative technique was employed in conservative ovarian surgery.

2. Changing technique resulted in only a small decrease in the incidence of rapid and painful cystic formation in remaining ovarian tissue.

3. During this three-year period, 9 of 26, or 35 per cent, of my cases required secondary operative removal of all remaining ovarian tissue. This was also necessary in 20 other cases.

4. In the six-year period, 1935 through 1940, with follow-ups through June, 1941, of 57 women who lost a part of their ovarian tissue none has required subsequent operation and only 2 have shown evidence of pathology of remaining ovarian tissue. This result is attributed to the routine postoperative use of estrogenic substance as described. This assumption is further borne out by the fact that operation has been avoided in 40 per cent of other women who presented themselves with discomfort or pain from early postoperative cystic formation.

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Of 432 operations on the Fallopian tubes for the purpose of sterilization, there were no failures by the Irving technique; of 50 cases there was one failure by the Pomeroy technique.

WILLIAM C. HENSKE.

THE USE OF STILBESTROL IN THE MANAGEMENT OF THE MENOPAUSE

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SINCE the introduction of stilbestrol,* there have been many somewhat conflicting reports on its toxicity and the clinical response to its use. Nausea, as a sign of possible toxicity, has been reported variously as occurring in from none to 80 per cent of the cases treated, and vomiting in from none to 32 per cent of the cases.¹ In the management of the menopause, investigators have almost invariably reported a certain number of cases in which they were unable to relieve the symptoms with stilbestrol. The findings in the treatment of this group of patients are not in accord with many of these reports.

MATERIAL AND METHOD

Our series represents 119 cases, of which 101 were at or beyond the menopause and 18 were younger women with a diagnosis of hypovarianism. Of the 101 patients in the menopause group, 67 were natural and the remaining 34 had a menopause induced by surgery or radiation. The 18 younger women included 11 cases which presented either continuously or cyclically, mild to moderately severe symptoms of secondary ovarian failure. These cases are included with the menopause group, bringing this to a total of 112.

The clinical response in all patients treated was correlated with the systemic estrogenic response as revealed by the vaginal smear. An "adequate response" to therapy, as reflected in the vaginal smear, was sufficient to produce an absence of deep "atrophy" cells with very small nuclei, a marked diminution in the number of leucocytes and a preponderance of cornified epithelial elements. The smears were interpreted by the pathologist who was not aware of the identity of the patient or the status of therapy. Some patients received only oral medication, others received the drug intramuscularly and still others by both routes, either singly or concurrently. The dosage of stilbestrol varied in the oral therapy from 0.05 mg. to 2 mg. daily and in the parenteral therapy from 0.1 mg. to 15 mg. per week. The duration of treatment was from two weeks to ten months.

*The stilbestrol used in this study was furnished through the kindness of The Department of Medical Research, The Winthrop Chemical Company, Inc.

MENOPAUSE

This group of patients presented the typical menopause syndrome of hot or cold flushes, headaches, nervousness, dizziness, emotional instability, insomnia, and various vague aches and pains. In addition to these symptoms, 9 patients complained also of pruritus and dyspareunia which was associated with a senile vaginitis. Several of this group of patients had an associated hypertrophic arthritis which had responded favorably to previous natural estrogen therapy. One patient, with an involutional melancholia, who had not responded to as much as 100,000 I.U. of estrone each week, was well controlled with 1.5 mg. of stilbestrol by mouth daily.

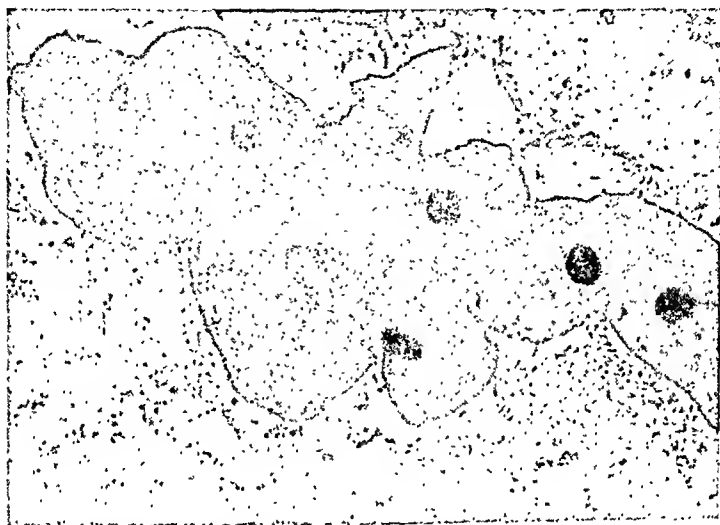


Fig. 1.—Photomicrograph (high power) of a typical menopausal vaginal smear, showing the oval squamous epithelial cells with large nuclei and many polymorphonuclear leucocytes. This smear was made from a woman who presented typical menopausal symptoms.

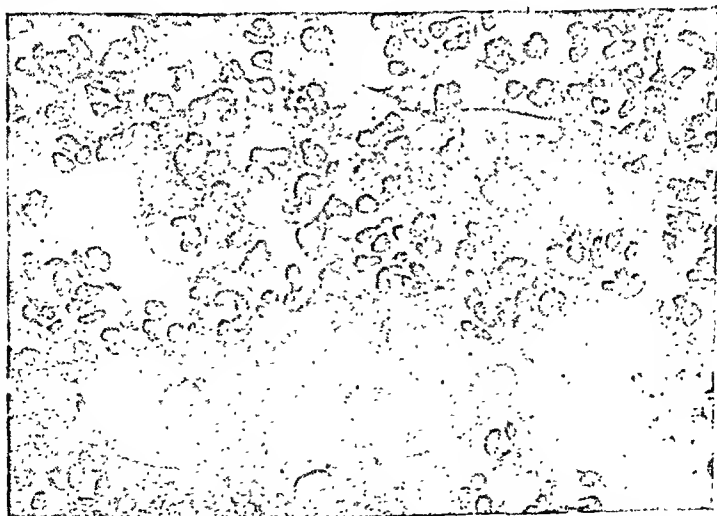


Fig. 2.—Smear from the same patient after relief of symptoms with stilbestrol therapy showing an adequate response. Note the absence of leucocytes and the cornification of the squamous cells.

The results in the group of menopausal patients can be briefly stated. In no case in which there was an adequate response in the vaginal smear was there failure to relieve the patient.

MISCELLANEOUS

This group included three young patients with a secondary amenorrhea which probably represented, in each case, a premature ovarian failure. These patients had failed to respond to pituitary gonadotropic hormone and thyroid therapy. Stilbestrol was used merely to produce estrogen withdrawal bleeding. This was accomplished several times in each case with oral doses varying from 1 to 2 mg. daily, for a period of from three to six weeks. These patients all noted a feeling of well being for the duration of stilbestrol therapy.

One patient presented herself with a history and physical findings of a functional menstrual irregularity. She was flowing profusely at the time of her visit. In an effort to stop the bleeding, she was given 1 mg. of stilbestrol intramuscularly and 1 mg. orally for six days. She reported that the bleeding stopped after 3 oral doses and that she had no further bleeding for eleven days. She did not return again to the clinic.

One patient complained of severe headache associated with her menstrual periods. During one menstrual cycle she was given 1 mg. of stilbestrol intramuscularly twice each week. She noted no improvement.

Two cases of primary amenorrhea in women, aged 23 and 21 years, were studied. Both patients presented, on pelvic examination, an infantile cervicouterine ratio, and biopsy revealed an atrophic endometrium. These patients were treated for seventeen and thirteen months, respectively. The endometria of both patients showed marked estrogenic response and the uteri approached adult size. The first patient menstruated 9 times without withdrawal of stilbestrol, and the second patient menstruated only 3 times, once apparently spontaneously and twice only after stopping the medication. The dose of stilbestrol in these cases was 1 mg. twice weekly, parenterally, and 1 mg. daily by mouth, respectively.

The last patient in this group was treated with large doses of stilbestrol, as Lissner² has suggested, in an attempt to influence a marked, unexplained virilism. She received, within a period of 110 days, 158 mg. intramuscularly and 41 mg. by mouth. No change was noted in her hypertrichosis, but there was considerable enlargement of the breasts; and the endometrium and vaginal mucosa showed a marked estrogenic response.

SIDE EFFECTS

Nausea occurred in 23 patients. Three of these patients also vomited. Six patients seemed to develop a tolerance to the drug, and as therapy was continued the undesirable effects disappeared. In some of these, the dose of the drug was decreased for a few days and then restored to its original amount. Nausea or nausea and vomiting were severe enough to demand discontinuance of therapy in 7 cases, or 5.9 per cent.

Postmenopausal uterine bleeding occurred during treatment in two cases. This was not troublesome, because it was possible to adjust the dosage so that no bleeding occurred and yet the symptoms were relieved.

No other undesirable or toxic effects were noted.

CONCLUSIONS

The estrogenic effect of stilbestrol is similar to estrone.

The indications for the use of stilbestrol are the same as for estrone.

Nausea and vomiting are apparently an individual idiosyncrasy. Some patients evidently develop a tolerance to this effect.

The optimum dose is from 0.5 to 1 mg. by mouth daily and 1 mg. intramuscularly.

Stilbestrol should be used only at the direction of a physician.

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Seimeanu, A., and Adamesteanu, C.: *The Pathogenesis of Perineal Pruritus and Its Treatment by Epidural Injections of Magnesium Sulphate*, *Presse méd.* 47: 1498, 1939.

Within four and a half years the authors saw 51 cases of idiopathic perineal pruritus in 65,000 gynecologic consultations at a Hospital in Bucharest. Cases of pruritus of a known etiology are not included.

Previously the authors had used local medications, autohemotherapy and physiotherapy. In this series all rebellious cases of idiopathic perineal pruritus were treated solely with epidural injections of 20 per cent magnesium sulfate.

The writers maintain that perineal pruritus is a syndrome capable of being induced by a number of factors (endogenous and exogenous intoxications and endocrine disturbances) acting upon the sympathetic nervous system in general but chiefly involving the sacral sympathetics. These irritative factors produce an imbalanced and sensitive sympathetic system, localized by an altered psyche to the perineo-genital zone, normally the location of voluptuous sensations. The psyche of the affected individual becomes aware of the increased voluptuous sensations which are then interpreted as a pruritus.

The centripetal path of perineogenital sensation is the sacral sympathetics which probably exhibit a biochemic imbalance in their structure, characterized by a decrease in the magnesium ion.

The writers inject 5 to 6 c.c. of freshly prepared, sterile, 20 per cent solution of magnesium sulfate into the epidural space, using the Cathelin technique. The patient remains on the table for fifteen minutes after the injection. The injection is repeated every third day for a total of 4 to 5 times in the majority of cases. A few cases required as many as 8 to 9 treatments.

The results are listed as follows: failure in 5 cases; 10 other cases had been observed less than six months and are not included in the final figures; in 36 other cases, observed six months to five years, 13 per cent evidenced mild recurrences at time of menses or following the use of coffee, while 87 per cent remained free of their perineal discomfort.

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Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

MENTAL DISORDERS ASSOCIATED WITH CHILDBEARING

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(Continued from page 163, January issue.)

PSYCHOPATHIC PERSONALITY (WITH AND WITHOUT PSYCHOSIS)

Psychiatric classifications contain an ill-defined group termed "psychopathic personality" (older term "constitutional psychopathic inferiority") which embraces a host of personality deviations. Ordinarily, these individuals are not actually psychotic but the warping of their personality and difficulties in adjustment are so severe as to warrant classification as abnormal individuals. In this group have been placed those individuals whose unstable, erratic, and impulsive behavior, emotional instability and antisocial attitudes bring them into conflict with established law and order. Some believe that the personality and emotional deficiencies are constitutionally determined; others maintain that unfavorable and emotionally warping influences in early years are the most important etiologic factors. Whatever the cause may be, the final personality pattern is unwholesome and poorly designed for social adjustment. Among the outstanding features of this personality pattern are selfish egocentricity, untruthfulness, disregard of the rights and opinions of others, cruelty, extreme self-assertion associated with a complete lack of foresight or ability to profit by past experience. Often these individuals are of normal or above average intelligence but still are unable to control their instinctive, impulsive behavior.

The defects of this personality pattern are usually manifested in childhood or adolescence but sometimes do not become fully apparent until early maturity when the individual is emancipated from parental dominance and protection. Often their limited capacity for adjustment does not become apparent until the increasing social and vocational demands of early adult years exceeds their meager adaptability. When this occurs, the individual responds with violent, antisocial, selfish, and cruel reactions instead of utilizing more socially acceptable and mature methods. Pregnancy and the responsibilities of parenthood may supply just this test of personality adequacy. In addition, sexual precocity and indulgence are frequently noted in this personality type and extramarital pregnancy is of common occurrence. When these individuals become pregnant, either maritally or extramaritally, their behavior is

marked by the same impulsive and egocentric trends which have been demonstrated throughout their earlier years. Occasionally, the novelty of the first pregnancy may be sufficient to inhibit their instability temporarily but later gestations will disclose their psychopathic personality organization. In response to severe strains such as pregnancy, these vulnerable personalities may break over into short, atypical psychoses which fade out, leaving the unwholesome character pattern as a residual. For these individuals, pregnancy is another difficult life situation to which they react in their customary manner.

CASE 5.—A single woman, aged 24 years, gravida i, was admitted to a home for indigents because of inability to work due to her pregnancy. Physical examination revealed a normal pregnancy in the sixth month without evidence of associated organic disorder. However, her conduct led to serious doubts regarding her sanity. She was extremely sensitive, easily irritated, and had temper tantrums without apparent provocation. At times she became unmanageable, showing a violent response to simple situations which could not be reasonably a cause of irritation. She maintained that the matron persecuted her and made life miserable and she resented everyone. For example, she became irritable when her room was not cleaned in the manner she desired and struck her roommate across the mouth although this girl was not bothering her. Her behavior at the dining table caused apprehension among her fellow lodgers because of her violent spasms of rage and recrimination, maintaining that they sucked their teeth and talked of their diseases and operations for the sole purpose of increasing her nausea of pregnancy. It was necessary to give her a single room and allow her to eat alone because of her surliness. When another resident admired her pretty clothes, she became incensed because she believed that these remarks of admiration were an insinuation that she was a prostitute "who had some rich, gray-haired old guy buying her clothes." She locked herself in the bathroom and occupied herself with sewing, regardless of the inconvenience to others. When asked to leave the bathroom, she threatened to stab the matron with scissors if she were touched. These are only a few examples of the irritability, sensitivity, and explosiveness displayed by this patient.

The history revealed that the above behavior was a continuation of her lifelong pattern. She was born in the South of a schizophrenic mother and shiftless, unstable father, and she learned early to respond to any untoward situation by antipathy and violence. When the patient was 10 years of age, the mother was sent to a mental hospital and the child regarded this with equanimity for "my mother always hated me because my father loved me so much and was willing to do anything for me." At 12 years of age, she was placed in an orphanage for "my stepmother hated me because she was jealous of me," but other information reveals that she was incorrigible, had temper tantrums and irritable outbursts and would not account for her nightly absences from home. At 14 years of age, she was sent to the home of an uncle and her temper tantrums and erratic behavior soon caused a marital separation "because he liked me so much that my aunt was jealous and hated me." She then secured work as a housemaid, usually being discharged from her position after one or two days. If the employer made suggestions or criticized her, she became enraged, even quarreling with small children. She was frequently admitted to indigent homes because of inability to hold a job. Between the ages of 19 and 24 years, she was admitted to hospitals at least five times for vague complaints and illnesses for which no organic basis could be found. It is not known when her sexual promiscuity began. When she learned of her pregnancy she had a violent temper storm and drove her paramour away because he was a shiftless drunkard.

Delivery was uneventful but the patient soon became difficult to manage. She talked sentimentally of the baby's need for a mother and how beautifully she would clothe her. A moment later she would speak of her intention to become an opera star or a fashionable mannequin or to enter some other type of work which was obviously far beyond her abilities. She enjoyed making sarcastic, cutting remarks about other patients, called them foul names and incited one against the other so

that she might enjoy the quarreling that ensued. She maintained that she was only an average girl and had no idea why everyone was so "mean" to her. According to the patient, her difficulties in adjustment were wholly on the basis of "mean-ness and silliness" of all the other people in the world. A diagnosis was made of: Psychopathic personality; unstable, explosive, antisocial type.

It is obvious that these women are incapable of wholesome motherhood. Often they vent their hostility on the newborn child by rejection, inattention to its needs, or even by slapping and cursing the infant because it represents an obligation and responsibility. Treatment of these patients is ineffectual and punishment does not act as a deterrent.

PSYCHONEUROSES

The psychoneuroses resemble the psychoses in that they represent symbolic physical and mental expressions of underlying emotional problems. They differ, however, in that they do not include a definite break with reality; the patient realizes that the disorder is in himself although he may erroneously believe the difficulty to be physical in nature and finally, although the sufferer may be incapacitated, he still remains a socially organized individual. The symptoms of the neurosis have their genesis in some emotional dilemma in which the individual is urged on by powerful instinctive, pleasure-seeking, selfish motivations and yet held back by moral and ethical obligations. Pregnancy and motherhood with all their inconveniences, responsibilities, and demands for unselfishness are times of great vulnerability, especially for individuals already possessing a neurotic constitution.

The focal beginning of all neuroses is a state of anxiety; the precise type of neurosis depends on how the individual handles this anxiety. It may remain as a relatively pure "anxiety state" with such mental symptoms as apprehensiveness, states of panic or phobias such as fear of death, insanity, or impending catastrophe. Physical manifestations such as tachycardia, nausea, diarrhea, dyspnea, or dizziness are usually noted. Other patients will achieve mental peace by converting this anxiety into physical symptoms, such as anesthetics, paralyses, blindness, convulsions, etc., and this syndrome is designated "conversion hysteria." Still others will avoid the basic emotional conflict by obsessively contemplating a substitute idea which is painful but not so distressing or disorganizing as the original problem, or find relief by carrying out some compulsive ritual; this reaction pattern is termed "obsessive-compulsive neurosis."

In the present series of cases the best single index of neurotic diathesis was the prepuerperal personality of the patient. Nearly every one had a history of lifelong neurotic traits. Some were weak, clinging, inadequate individuals who always became disorganized when confronted with a difficult situation. Others were selfish, whining, querulous types who had temper tantrums whenever frustration appeared imminent. Still others were timid, apprehensive persons who had always been unusually concerned with their physical, mental, or moral health.

The neurotic patients in this series could be classified grossly in three groups if precise psychiatric diagnoses were disregarded and the cases studied from the standpoint of the genesis and form of their reaction pattern. In one group the neurosis appeared to be a natural outgrowth of the patient's personality deficiencies. These individuals were of a selfish, irritable, unstable type who were usually sexually and emotion-

ally maladjusted in their marriage. The neurotic symptoms appeared after the first delivery which was neither complicated nor unusual. These patients were never well thereafter, becoming irritable, petulant women with innumerable pains and a host of visceral disturbances. Usually there were episodes of extreme anxiety with fears of impending death, prolonged bouts of weeping and self-pity and disinterest in the home and children because of pathologic preoccupation with their own symptoms. Each ensuing pregnancy added an increment to the symptoms until a pattern of chronic neurotic invalidism was established.

CASE 6.—A married woman, aged 24 years, para ii, was admitted to the hospital six weeks after her second delivery. She had remained in bed since this delivery, wept frequently, had episodes of irritability, and complained of pain in nearly every part of the body.

Physical examination revealed a well-developed, well-nourished woman. There was no evidence of physical disorder and laboratory studies were negative. The patient was apprehensive and tense and made a constant effort to win the sympathy of the physicians and nurses. She complained of palpitation, numbness of the arms and legs, and pain in the back. Frequently she berated her husband, stating that he should not have allowed her to become pregnant, that he was not attentive enough, and that he preferred to be with other people rather than to attend to her needs. At times she feared that she had some incurable physical disease and at other times had a phobia of oncoming insanity. There were many episodes of self-pity and weeping associated with a repetitious enumeration of her many symptoms. She found many excuses for her own shortcomings, stating that the second pregnancy was "just too much for me" and "I should never have been allowed to become pregnant with my womb in such bad condition." When her attention was momentarily diverted by some entertaining event, she became interested, vivacious and friendly but relapsed a few moments later into her weeping, complaining behavior pattern. A diagnosis was made of: Psychoneurosis; anxiety hysteria.

The family history was negative for any mental abnormality. The patient was the youngest of eleven siblings and was petted and waited upon as the baby of the family. The menarche occurred at 12 years of age; the menstrual periods were painful and associated with nervousness and irritability. She completed high school, was a popular girl, and always had many friends. At home she was dictatorial, disliked anyone who disagreed with her, and was always dissatisfied although she was given luxuries beyond the family means. She loved to dance, to attend social functions, and to be entertained and demanded expensive, fashionable clothing. Whenever her wishes were not immediately granted, she had a bout of weeping and depression or else became disagreeable and sarcastic. After completing school she worked as a clerk for a short time but left this work to remain at home where others would wait upon her.

She married at the age of 21 years to a steady, dependable man who gave her everything possible within the limited means of his small salary. The first pregnancy occurred shortly after marriage and her health was excellent throughout gestation. The delivery was difficult and required instrumental assistance. Her post-puerperal convalescence was very slow, and she had many complaints with no apparent organic basis.

The second impregnation occurred two years later and was contrary to the patient's wishes. As soon as she learned of the pregnancy she became apprehensive and irritable and complained of pelvic pain, faintness, dizziness, and palpitation of the heart. After the second delivery, which was easy and uneventful, her symptoms became innumerable. She refused to leave her bed, was careless and disheveled in appearance, and wept when confronted with any household task. It became necessary to send the children to the grandparents because of her neglect and disinterest, and the husband had to do the housework and cooking. She complained constantly of her symptoms and became indignant if the family would not listen and accused them of callousness, sobbing that they had never done anything for her. Episodes of

uncontrolled laughing and weeping occurred. Numerous physicians were in attendance, the patient discharging each one as soon as he suggested that she had no physical disorder and should resume her domestic duties.

In the hospital the patient was unable to sleep and complained constantly. With psychotherapy she slowly gained insight into her selfishness and the defensive aspects of her illness. She soon was able to face the fact that her illness was not physical in origin but was really an effort to avoid the monotony and responsibility of an adult maternal routine. She was discharged after one month of hospital residence. Three years later the husband wrote that his wife was "a changed woman—perfectly healthy and interested in her home and children."

The second group included those individuals of an unstable personality who were able to make a fair life adjustment until confronted with some puerperal problem or conflict with which they were unable to cope. In this group were such cases as hysterical convulsions and chorea in a timid, dull single girl who found herself pregnant, and prolonged hysterical stupor in an unmarried woman after several bungling, painful attempts at abortion. The following case illustrates the development of such a syndrome:

CASE 7.—A married woman, aged 20 years, para i, gravida iii, was admitted to the obstetric ward because of pain in the right lower quadrant of the abdomen, nausea, chills, and sweating. These symptoms began on the day of admission but the patient had been "nervous" throughout gestation. The first pregnancy terminated in a normal delivery; the second ended with miscarriage at three months.

Physical examination disclosed a well-developed, well-nourished woman who was not acutely ill but whose facial expression indicated great pain. The blood pressure was 115/80. Further examination was negative except for pregnancy nearly at term. Urine examination revealed a trace of albumin and numerous white blood cells but other laboratory studies were negative.

On the second day after admission, the patient had a convulsive seizure with twitching of the mouth and dorsiflexion of the head and spine. This attack was synchronous with the onset of labor. Six hours later there was another convulsion of five minutes' duration, the patient assuming the opisthotonos position. After one minute of relaxation, a similar seizure occurred lasting seven minutes. During these attacks there was marked respiratory embarrassment and cyanosis. A short time later the uterine contractions ceased and no further convulsions occurred. Repeated examinations failed to reveal any evidence of a toxemia of pregnancy.

Psychiatric examination revealed a cheerful young woman who appeared to be in good physical condition. She was not very intelligent and her reactions suggested that she came from a low socioeconomic and cultural group. The patient had been reared in a small town in a strict, religious environment and was taught that sexual transgression was the greatest possible sin. At the age of 17 years she had a sexual relationship (the patient stated that she had been raped) and soon discovered that she was pregnant. The father of the child treated the matter as a joke, told everyone about it and finally decamped, leaving her the object of scorn and ridicule throughout the community. When she informed her father of the pregnancy, he ordered her from the home. She went to another town, in a state of anxiety and tension, and entered a hospital for delivery, telling numerous protective falsehoods. The delivery was uncomplicated, but the child was deformed, having a myelencephalocele, spina bifida and talipes. She regarded this as God's punishment for her sins. After discharge from the hospital she was desperate, fearing to return home with a sick, deformed child. She left the child on a doorstep, excusing herself by thinking that it would get more medical attention in this way. The baby was traced to her by the footprints and a greater scandal occurred, and she was brought to trial for child neglect and desertion. Although acquitted by a kindly judge who felt that she had already suffered enough, her unpopularity in the community only increased. The child was a constant care but its death at six months seemed to

her to be the final payment for her sin and guilt. She became highly hysterical, fainted many times, and "jerked all over."

A short time later she married and, although she loved her husband, she was sexually frigid. She became an invalid and each time she saw a picture of the dead child she fainted or had screaming spells, usually being ill for several days. There seemed to be no way of reaching peace and happiness at home, and she could gain relief from her feelings of guilt only by going to church and praying for hours for forgiveness and another child. These reactions were intensified when her second pregnancy ended by miscarriage.

During the present gestation she was obsessed by a constant fear that God would punish her by great pain or even death. In addition, there was a tremendous fear that this child would be malformed as her culminating punishment. When she came to the hospital she was uncomfortable and frightened because of cystitis of moderate severity. With the onset of labor, her underlying anxieties became unbearable. She stated that she became overwhelmed when these intolerable feelings of tension and fear reached a certain intensity and these emotions were then transformed into a convulsive seizure.

Psychotherapy of an explanatory and reassuring type produced a rapid and satisfactory improvement. After unburdening herself of her fears and feelings of guilt, she was able to look forward to delivery with confidence and tranquillity. No further abnormal behavior occurred, and she was discharged from the hospital after five days of residence. She delivered a healthy child at home and was apparently a cooperative patient except for one or two "slight spells of nervousness." Her postpartum course was uneventful except for recurrent pyelitis but no further neurotic manifestations occurred. A diagnosis was made of: Psychoneurosis; conversion hysteria.

This group also included women who were confronted with a difficult economic situation complicated further by repeated pregnancies. After seven or eight pregnancies their physical reserve was depleted, their socioeconomic status precarious and their life one of drudgery and constant attendance to an ever-increasing family. Another pregnancy served as the final straw, the patient developing a psychoneurotic illness in the face of this intolerable situation.

The third group included highly complex neuroses which were the expression of deep emotional conflicts and attitudes of guilt due to the sexual aspects of the pregnancy. The physical and physiologic disturbances of gestation appeared to play no role in the genesis of the syndrome. Rather, the conception and delivery of the child seemed to have a deep psychologic significance and revived latent conflicts and problems which usually were concerned with sexual sin, guilt, and distorted emotional attitudes of childhood years.

CASE 8.—A married woman, aged 29 years, para ii, was admitted to the hospital one month after the second delivery because of suicidal gestures and two murderous assaults upon her son, aged 4 years. The last delivery, occurring in the seventh month of gestation, was uncomplicated and the hospital course was uneventful. The infant died after one day. While in the obstetric ward, the patient appeared depressed, refused her medications, and insisted on leaving on her ninth day. She remained in bed at home for two weeks and often spoke vaguely about the authorities coming for her. The episodes of weeping became more frequent, and she blamed herself constantly, stating that she had caused the miscarriage by overwork. In the next few days she refused to eat, had persistent insomnia, and cut up ropes with which to hang herself, although she made no actual attempts. On one occasion she locked herself in the bathroom and threatened to drink poison; once she stood before her husband and drew a cord tightly about her neck but released it when she be-

gan to strangle. Shortly before admission she suddenly assaulted her son and the next day she again strangled him, the child being cyanotic and limp when the husband intervened.

Physical examination revealed a well-nourished, stocky woman who was in excellent physical condition. Neurologic and laboratory studies were completely negative. The patient was shy, embarrassed, and somewhat depressed. She stated that she had lost all interest in life and everything seemed different and without meaning. Her greatest concern was the fear that ideas might come to her to harm someone and that she might carry out these impulses. When she thought of the possibility of inflicting some cruel injury upon others, she became terrified. These obsessive thoughts recurred constantly and caused her much anguish, the patient stating, "Doctor, my heart must be just full of murder." She was afraid to return home lest she carry out these sadistic, compulsive urges. A diagnosis was made of: Psychoneurosis; obsessive-compulsive neurosis with secondary depressional reactions.

The family history was negative for mental abnormality. The family were a lower class English group and had spent much time "on the Dole." The father was a strong-minded, domineering individual who taught the patient to repress sternly her own emotions and personality and accept whatever treatment her superiors dispensed. She spent much of her girlhood "in service," was mistreated and abused but learned to accept it with docility although she inwardly raged. Her sexual interests were early aroused but were rigidly repressed because she believed them to be sinful. All these factors contrived to make her timid, fearful, self-effacing, over-conscientious, and meticulous. At 17 years of age she was seduced or raped by the husband of her mistress. She was extremely frightened and felt guilty but was incapable of defending herself and was afraid to tell her rigidly moral family. After repeated relationships she became pregnant and the employer forced her to have a criminal abortion. She became seriously ill, had a fever of 104° F., and was constantly obsessed by the thought: "I've murdered a child." Later her employer resumed the relationships and she often thought of committing suicide because, while she resented his assaults, she was too timid to defend herself or to expose his behavior.

At the age of 20 years, she married a stable, devoted man. He found her to be sensitive, easily hurt, anxious, and always requiring encouragement and reassurance. Her first pregnancy and delivery were uneventful. A few weeks after delivery the thought suddenly came to her: "I might murder this baby." She became frightened that she might have the impulse to strangle him and was afraid to be alone with the child. She spent her days on the streets with the infant in his carriage so that passers-by could stop her if she made a homicidal attempt. To her husband she complained of a choking sensation in the throat and intense nervousness and expressed the fear that she could not "bring up the boy." Several physicians were consulted because of "nervousness" but none ever asked why she was emotionally disturbed and each merely prescribed a mild sedative.

The next pregnancy, four years later, was planned. Severe nausea and vomiting occurred in the third month and she later complained of severe uterine pain and choking. She frequently expressed the fear that she would "lose the baby" before term. When this actually happened in the seventh month, her feelings of guilt and responsibility were severe and painful. The belief that she had killed another baby was distressing, but it was soon replaced by the terrifying obsessive fear that she might strangle her son. Finally, in two periods of mental unclarity, she actually attempted to carry out this compulsion.

Prolonged hospital residence with extensive psychotherapy and convulsive shock treatment produced a satisfactory improvement in this patient. It was felt that she was a vulnerable individual and that further pregnancies might precipitate another severe mental disturbance.

The psychoneuroses associated with childbearing are probably more numerous than our statistical tables would indicate, but the majority

are never seen by psychiatrists. Usually they drift into a chronic neurotic state and present a constant problem to the obstetrician. During gestation they have innumerable complaints and inexplicable symptoms and not infrequently demand therapeutic interruption of the pregnancy. In the state of our present knowledge, such termination is unjustified. It will not cure the neurosis and may even aggravate the neurotic disorder because of associated feelings of guilt and remorse.

The prognosis of the psychoneurotic patient will depend on her personality assets and the psychotherapeutic treatment she receives. A fair number will make a spontaneous social recovery once the strain of pregnancy is removed, but the recovery rate will be materially increased by psychotherapeutic efforts on the part of the physician. Practically all these patients, whether recovered or not, will be able to live in the community, some as chronic neurotic invalids, others as unhappy, physically uncomfortable "nervous" women. The neurosis is liable to return or to be exaggerated by further pregnancies which add to the patient's life burden.

EPILEPSY

Pregnancy may be related to epilepsy and its associated psychoses in two ways. In the first instance, pregnancy may occur in an epileptic patient and may improve, aggravate, or not affect the convulsive disorder, but it is impossible to predict its effect in any given case.¹⁰⁵ The patient with a paroxysmal convulsive disorder, whether pregnant or not, is liable to episodic mental disturbances, such as psychic equivalents, postconvulsive confusional states, etc. Occasionally, these mental disorders occur in the pregnant epileptic patient, but the psychosis is due to the paroxysmal convulsive disorder, not to the pregnancy which acts only as an aggravating factor.

The second possible relationship between these two disorders is when the initial convulsion occurs during pregnancy, marking the beginning of an epileptic syndrome. The convulsive disorder then runs its own course, sometimes marked by psychotic episodes and eventuating in intellectual and personality deterioration. Again, the mental disorder is a part of the convulsive syndrome, the pregnancy serving only as the precipitating factor. In both instances, it would be incorrect to ascribe any specific effect to the gestation inasmuch as all these mental disturbances are seen both in epileptic men and in women with convulsive disorder who have never been pregnant.

Certain practical problems may arise in the pregnant epileptic patient. A convulsive seizure occurring in late gestation may be incorrectly diagnosed as eclampsia and unnecessary obstetric procedures instituted. A history of previous convulsive attacks and negative findings of toxemia would suggest the correct diagnosis. Another difficult problem is presented by the patient whose epilepsy is severely aggravated by pregnancy and whose mental deterioration seems to be accelerated by repeated childbearing. Sterilization is indicated if the patient's mental and nervous health is suffering severe impairment. Induced abortion for eugenic reasons is not justified in the state of our present knowledge concerning the hereditary aspects of epilepsy.

ACUTE SITUATIONAL REACTIONS

Certain patients may display sudden excited, often violent, patterns of behavior which defy psychiatric classification in response to the acute

psychologic situation caused by pregnancy. These appear to be due to an increasing accumulation of tension and anxiety in relation to the situation with a sudden discharge of this energy in violent, disturbed behavior, often directed toward the injury of others. One type of reaction is the "Frenzy of Montgomery" of the older obstetricians. This occurs when the head sweeps across the pelvic floor and dilates the vulva, the patient becoming highly excited, cursing profanely at the physician, and being extremely difficult to control, but within a few moments regaining composure and apologizing for her behavior. Another type is the explosive excitement, uncontrolled behavior, prolonged weeping, or impulsive efforts at self-destruction of the unmarried woman who finds herself pregnant. Similar types of uninhibited, excited behavior may be manifested by the married woman who fears another pregnancy. It is quite possible that some of the impulsive infanticides occur in this manner, especially in unmarried mothers who cannot face the stigma associated with return to their own communities. The desertion of children, as shown in Case 7, may occur on the basis of panic and desperation in the face of an acute, intolerable situation. These behavior patterns can often be better comprehended as understandable reactions of a desperate and frightened human being rather than as psychiatric entities. Usually the disturbed behavior is of short duration, often disappearing immediately when a solution for the situation is found.

DIAGNOSIS

It requires no diagnostic acumen to recognize the presence of a puerperal mental disorder but this gross diagnosis has neither therapeutic nor prognostic value. For these purposes it is necessary to make an early and precise psychiatric diagnosis and this is often difficult in an excited and confused patient because of the amorphous character of the reaction. In some cases a history of previous attacks of mental disorder with a description of the psychotic behavior and subsequent course may establish the diagnosis. The time of onset of the psychosis, whether gestational, puerperal, or postpuerperal, is usually of little diagnostic value. It has been shown⁶⁶ that certain mental disorders are most likely to begin in the first week postpartum, while others more usually appear at the end of three weeks, etc. However, it must be realized that these figures are statistical averages and are not a valid basis for diagnosis in an individual case.

The best method of reaching a correct diagnosis is by a minute study of the lifelong personality and a careful evaluation of the clinical psychiatric picture, seeking for major trend patterns. The physician is prone to overvalue the less important symptoms of mental clouding and confusion and to make an erroneous psychiatric diagnosis of a toxic state. The greatest number of mistakes are made in diagnosing a "toxic psychosis" when, in reality, the confused state is merely masking the underlying manie-depressive or schizophrenic disorder. Even the presence of a physical state of toxicity is not conclusive evidence that the accompanying psychosis is a toxic delirium. Inasmuch as the whole plan of treatment, the problem of future pregnancies and the management of the patient after recovery are dependent upon a correct diagnosis, it is essential to have competent psychiatric consultation.

PROGNOSIS

The prognosis for recovery of the whole group of major puerperal psychoses is about 70 to 75 per cent.^{82, 92, 96} This figure means only that

nearly all the manie-depressive and delirious patients and a few of the schizophrénies will recover. It is not correct to state that any puerperal case has a 75 per cent chance of recovery inasmuch as the actual chances are much less if she has a schizophrénie psychosis.

TREATMENT

The early recognition of the presence of a puerperal mental disorder is of greatest importance in the correct management of the case. Too often the attending physician unconsciously refuses to admit the existence of a psychosis or allows the patient to drift into a deplorable condition while he misleads himself with the naïve and wistful hope that "everything will be all right in a day or so." Due to the constant overactivity, excitement and uncooperativeness, these patients rapidly become toxic, exhausted, dehydrated, and malnourished with consequent prolongation of mental convalescence.

The therapeutic efforts of the attending obstetrician should be directed toward the protection of both the mother and child from injury and attempts to improve the maternal physical health as rapidly as possible. Any infection or toxic condition should receive appropriate treatment. The patient should be placed in a secure, serene, single room at once and constant nursing supervision be maintained to prevent suicide or escape. Every effort should be made to avoid physical restraint by supplying adequate nursing service. Exhaustion should be prevented by the judicious use of sedatives, changing the drug frequently to avoid cumulative effects. The state of nutrition should be watched carefully and tube feedings instituted at once if sufficient nourishment is not taken. If dehydration occurs, intravenous infusions should be utilized. Blood transfusions should be used when indicated. Usually it is wise to place the baby on a feeding formula and to suspend maternal mammary function, inasmuch as it will be an exhausting procedure to attempt to empty the breasts, and it is not safe to allow the infant to nurse.

No specific therapy has proved to be of any value. Occasional successes have been reported with hormone therapy, but there is no valid evidence of its efficacy and other physicians have been unable to duplicate the results. Some investigators, believing that an otherwise asymptomatic infective process was causing the psychosis, have used mixed vaccines.^{63, 65} This form of therapy probably has little value.

Psychiatric consultation should be secured at the earliest possible moment. Usually a more rapid convalescence will occur if the patient is transferred to a mental hospital where appropriate psychotherapeutic measures can be instituted.

PROBLEMS OF MANAGEMENT

The question of induced abortion is always raised in those cases in which mental illness and pregnancy occur synchronously. This problem is too frequently approached with little actual data and the decision is made on the basis of the physician's personal predilection and bias. There is really only meager information on which to base conclusions. If pregnancy occurs in a patient already mentally ill, there is no way of predicting the effect of this gestation; some patients may show mental improvement, others become worse. No one can safely predict the effect of abortion in these cases. Some patients may improve when the strain of pregnancy is removed; many remain the same, while others become

worse. In 1933, Robinson⁸² polled 95 British psychiatrists and an overwhelming majority believed that abortion in these cases was not justified. The same general opinion was held for those cases of mental disorder appearing during pregnancy. There appeared no conclusive evidence that the mental illness would be ameliorated by induced abortion and some felt that it might be made worse by the operative shock and emotional upheaval sometimes associated with this procedure.

At the present time, the majority of physicians believe that abortion is justified only when the maternal physical or mental health is in jeopardy. There is little evidence proving that induced abortion has a therapeutic value in arresting the development of a mental disorder in predisposed individuals or those already suffering from mild mental disturbances. Furthermore, the majority of puerperal psychoses spontaneously progress to recovery without permanent psychic damage. The final decision will depend upon the individual case but a positive conclusion should not be reached on the basis of a naïve belief that an abortion will solve the emotional conflicts, terminate a psychosis (except an obvious toxic delirium) or prevent a mild mental disorder from becoming worse or possibly permanent.

The question of termination of pregnancy in these cases is usually connected with the whole problem of induced abortion for eugenic purposes. It is usually argued that the child will probably be a mental misfit since the mother was mentally disordered. There is no valid scientific evidence that this is true. Our knowledge of the hereditary factors in the production of mental disease becomes less conclusive as we learn more about the factors of training, early environmental influences and psychologic conditioning. In view of the chaotic state of our knowledge concerning these hereditary factors, it becomes obvious that no one can predict with any certainty as to the mental caliber of these offspring, and destruction of the unborn on the basis of guesswork and superstition cannot be justified.

Whether these patients who have had puerperal psychoses should undergo further pregnancies often presents a difficult problem. Certainly no pregnancy should occur for at least two or three years after convalescence from the mental disorder. The final decision should be reached only after consideration of all factors. Among these are the patient's wishes and fears, her religious beliefs and possible feelings of guilt as well as all of the physical, physiologic, socioeconomic, and toxic factors which had etiologic significance. The type of psychosis from which she suffered will be of great importance in reaching a decision. Further pregnancies should not be permitted if a schizophrenic psychosis has occurred. Manic-depressive patients may have recurrent attacks of increasing severity, but cases have been reported with a psychotic episode in the first pregnancy and no further difficulty until the sixth gestation. Some psychoneurotic patients find their life load increased intolerably by repeated pregnancies and conception should be prevented before their meager capacity for adjustment is exceeded. On the other hand, if the patient has had a toxic psychosis, she may be able to withstand further gestations without psychic disturbances if the physical status is improved.

The patient's attitude and wishes regarding further pregnancies should receive consideration. A patient who has had a puerperal attack of mental disorder may be terrified at the prospect of another pregnancy. For these individuals, the marital life may become a torment

and the satisfaction and pleasure in sexual relationships ruined by the ever-present fear of pregnancy and its accompanying psychosis. Contraceptive measures may be satisfactory if the patient is intelligent and reliable and if there is no anatomic contraindication. However, the fear of contraceptive failure may be sufficient to ruin the marital happiness and serve as a constant source of apprehension. Sterilization should be undertaken if absolute contraception is necessary.

PRODROMAL MANIFESTATIONS

A study of case histories of puerperal psychoses reveals that usually warning signs appear during the gestational period. However, it is not always easy to evaluate the nervous reactions of a pregnant woman since many bizarre psychologic manifestations may occur without subsequent psychosis. Probably the best single index is the attitude of the patient to her pregnancy and any changes in this attitude which may occur during gestation. An attempt to produce an abortion is indisputable evidence that she does not desire the pregnancy. This rejection may also be expressed by prolonged bouts of weeping, expressions of rancor against the husband, or by irritable references to the unenviable position of women in general and herself in particular. Other indications of an unwholesome mental attitude are irritability, prolonged temper tantrums with little provocation, and evidences of discontent. One of the most common symptoms is increasing tension with excessive anxiety and concern over trivialities, the patient becoming apprehensive and panicky without adequate reason. Flightiness, disconnection in thought and speech, unwarranted suspicions and the occasional production of apparently meaningless, and irrelevant ideas are to be regarded with concern. Probably the most serious manifestation is a progressive, sustained change in personality, especially when it includes suspiciousness and withdrawal. Wide emotional swings from depression to elation may presage a manic-depressive episode. If the above manifestations are obvious and excessive, the physician should consider the possibility of an oncoming mental disorder, especially if the puerperium is associated with toxicity, exhaustion, or psychic shock.

PREVENTION

Modern medical opinion constantly emphasizes the treatment of the patient as a whole person rather than regarding him as a collection of malfunctioning organs operating in a social and emotional vacuum. The modern obstetrician no longer considers gestation to be solely a pelvic phenomenon but is interested in all of the interrelationships of the whole organism under the stimulus of pregnancy. At the present time, obstetrics has achieved a high standard in the physical care of patients, but insufficient attention has been given to the psychic aspects of pregnancy. The obstetrician is just as responsible for the prevention of mental disturbances in his patients as he is for the prevention of eclampsia.

The present discussion has suggested that not all women have reached a psychic and emotional maturity sufficient to withstand the impact of pregnancy and motherhood. While the physician cannot prevent the marriage and impregnation of these individuals, he can serve a useful purpose in two ways: He can promote a better standard of mental hygiene for the young women in his community so that they reach a simultaneous emotional and physical maturity, emancipated from dependence and unwholesome parental attachments, ready for a healthy

sexual marital adjustment and motherhood. Second, he can refrain from suggesting matrimony and motherhood as a cure-all for personality disorders and neurotic disturbances. Marriage and pregnancy impose new burdens upon the individual rather than relieve him of his previous disabilities and maladjustments. It would be more reasonable to advocate treatment of the personality disorder before exposing the already vulnerable individual to the strain of either marriage or pregnancy.

No obstetrician would wish to supervise a pregnancy without evaluating the cardiac and renal reserve and without knowing whether the pelvic outlet was adequate. He should be equally unwilling to bear this responsibility without some evaluation of the patient's psychic reserve. The initial history and all the subsequent discussions should be designed to supply answers to the following questions: What is her constitutional psychologic fitness for pregnancy and motherhood? What personality disabilities does she have which are a source of danger? What are the social, economic, marital, and moral problems and conflicts which confront her? What are her fears and anxieties? What is her real attitude toward this pregnancy and why does she have such reactions? What are the factors in her past life that shaped her personality—is the end result wholesome and capable of bearing stress, and, if not, how can it be understood and improved? Such a history will also reveal previous neurotic and psychotic episodes as well as lifelong instability and inadequacy. If time, tact, and patience are employed, the answers to these questions will be forthcoming, and it will be possible to outline a therapeutic program. There should be ample opportunity for the patient to discuss freely her fears and problems. Often merely bringing out these difficulties openly will give considerable relief, and common sense advice from the physician will solve most of the remainder. However, he should avoid a too critical and authoritative attitude since this often makes patients either resentful and uncooperative or so ashamed of their problems that they avoid discussion. Rather, he should attempt kindly understanding and should help the patient to find better ways of meeting her problems. At times, more direct action will be necessary. For example, if the husband's attitude or behavior is contributing to the unwholesome situation, the physician should not hesitate to discuss the matter frankly with him and attempt to enlist his cooperation. Whatever the problem may be, a wholehearted effort should be made to reach some solution before the time of delivery. Some problems may present an insoluble dilemma, but the patient may still be helped by a frank discussion and a wholesome change in attitude toward the unsatisfactory situation. If this program is followed, the patient will approach term with more confidence and stability and will be better able to withstand any untoward physical complications which may occur.

The obstetrician has shown that he is able to prevent most of the physical disasters of the puerperium. It is also his duty to assume an equal interest in the mental welfare of his patients, for as Gregory⁶⁰ has observed, "A sunny room and plenty of fresh air are not going to prevent the outbreak of a psychosis if the relationship toward the husband and the outlook for mutual respect and healthfulness are dark and humiliating. It is of little avail to give generous advice on the matter of physical hygiene and keep absolutely quiet about rotten social conditions . . . our constant effort must be toward the goal of better mental hygiene."

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Editorial

The Perpetuation of Error

THIS rather provocative title should call particular attention to the Chairman's Address at the last meeting of the section on obstetrics and gynecology of the American Medical Association.* The choice of subject is relevant and significant. Although the address may arouse favorable comment and likewise criticism, this should prove most desirable, and there is little doubt that the majority of thinking men will be in accord with the principles enunciated by Dr. Miller.

Errors are common enough in every field of endeavor. It is their perpetuation which constitutes a source of danger. Dr. Miller calls attention to numerous repetitious errors committed daily in the practice of our specialty, many of which are engendered by custom but for others he places the responsibility upon the sacrifice of quality in many contributions to medical literature. He feels very strongly that much of this can be traced to the insistent demands of department heads upon their often less mature staff members for "original research" articles. Many of these he claims are mediocre, digressive, and unsound; the conclusions which they present are insufficiently documented and inadequately checked. These contributions in Dr. Miller's belief perpetuate errors and false notions. Clothed as novelties, they, in addition, are readily seized upon by multitudinous lay writers who are flooding the popular magazines with their effusions. The latter may even mold public opinion beyond any control by the medical profession.

The fallacious assumption that the results observed in animal research can be transmitted directly to human experiences in gynecic practice, is another persistent error pointed out by Dr. Miller. For example, confusion has been added to confusion by the multitude of hormone preparations exuberantly reported upon by a multitude of observers. The impression is gained that, very frequently, these are subsidized by interested manufacturers, although it may be said in favor of the latter that their own well-conducted laboratories have added greatly to our knowledge in this field.

An advance must be acknowledged in this trend to corrective measures in diseases and disturbances of the female generative organs aside from those of a purely mechanical character which dominated and still dominate so much of gynecologic practice. The preservation of essential organs, in whole or in part, by the avoidance of radical pelvic surgery, unless definite pathologic evidence dictates the latter course,

*Journal of the American Medical Association, September 13, 1941.

requires that more intimate knowledge of physiologic relationships which has so often been ignored in the past because of erroneous principles based upon insufficient knowledge.

Dr. Miller's critical attitude toward delivery service as conducted in many homes or in poorly equipped hospitals is well taken. However there is no immediate solution and it must be admitted that the experiences of many general practitioners in obstetrics are better than those of many hospital services.

The general practitioners, especially in isolated communities, often far removed from modern hospital facilities, do not write in as boasting terms as do the urban specialists. Their results are good provided the initial make-up of the home-delivering doctor includes, as it does usually, integrity of character, certain technical ability, requisite patience and sound judgment.

We need not teach dual standards for home and hospital care. But the home delivery cannot at present be disregarded; it is inefficiency which needs be set aside in both instances. The hospital must still contend with tendencies toward interference, over-zealousness and radical management of labor.

Dr. Miller has spoken well and wisely. It remains for other teachers in this field to indicate the path of improvement and to eliminate what he so courageously describes as the perpetuation of errors in our particular field of medicine. Unfortunately this is duplicated elsewhere in perhaps equal volume.

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS, AND ABDOMINAL SURGEONS

*FIFTY-FOURTH ANNUAL MEETING, THE HOMESTEAD,
HOT SPRINGS, VA., SEPTEMBER 11, 12, 13, 1941*

The following papers were presented:

- President's Address. (Observation in the Art of Medical Illustration.)** Dr. Frederick H. Falls, Chicago, Ill.
- Gonadotropic Hormone Concentration in Emesis Gravidarum.** Dr. F. J. Schoeneck, Syracuse, N. Y. (For original article, see page 308.)
- Transverse Plication of the Rectum for the Reduction of Large Rectoceles.** Dr. Walter T. Dannreuther, New York, N. Y. (For original article, see page 286.)
- Management and Outcome of Labor in 742 Women With Borderline Pelves.** Dr. J. Bay Jacobs, Washington, D. C. (For original article, see page 267.)
- Malignancy of the Ovaries.** Dr. James R. Goodall, Montreal, Canada. (For original article, see page 210.)
- The Treatment of Gonorrhea in the Female with Sulfathiazole.** Drs. Dudley R. Smith, and Rogers Deakin, St. Louis, Mo. (For original article, see page 296.)
- Study and Management of the Cervix Before Hysterectomy.** Dr. Henry L. Darner (by invitation), Washington, D. C.
- Granulosa and Theca Cell Tumors of the Ovary.** Dr. D. Nelson Henderson (by invitation), Toronto, Canada. (For original article, see page 194.)
- Endometriosis.** Dr. Walter R. Holmes (by invitation), Atlanta, Ga. (For original article, see page 255.)
- A Study of 104 Cases of Uterine Fibroids Associated With Arterial Hypertension.** Dr. W. O. Johnson (by invitation), Louisville, Ky. (For original article, see page 231.)
- Pathology of the Embryo and Abortion.** Dr. A. K. Paine, Boston, Mass. (For original article, see page 245.)
- An Improved Method of Uterine Closure in High Classical Cesarean Section.** Drs. Milton G. Potter, and Norman W. Elton, Buffalo, N. Y. (For original article, see page 303.)
- Hysterectomy in Pregnancy, Labor and the Puerperium.** Dr. Gerald W. Gustafson, Indianapolis, Ind. (For original article, see page 221.)
- Occiput Posterior—A Normal Presentation.** Dr. L. A. Calkins, Kansas City, Mo. (For original article, see page 277.)
- A Comparison of Thyroid Extract and Iodine Therapy in the Prevention of Toxemia of Pregnancy.** Drs. Emmett D. Colvin, R. A. Bartholomew, and W. H. Grimes, Atlanta, Ga. (For original article, see page 183.)
- Midline Episiotomy.** Drs. J. P. Pratt, C. P. Hodgkinson, and C. R. Kennedy, Detroit, Michigan. (For original article, see page 292.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Physiology of Pregnancy

Bowman, Donald E.: The Use of a Reducing Factor of Pregnancy Urine in the Diagnosis of Pregnancy, *J. Lab. & Clin. Med.* 24: 1072, 1939.

To obviate time and expense, a chemical test for pregnancy would be of distinct value. Urinary pregnancy hormones are known to contain a reducing factor, and this substance might be developed for use in such a chemical test.

The technique of the test is as follows: 12 c.c. of a fresh specimen of urine, specific gravity 1.020, are brought to a pH of 7.4 with 10 per cent sodium hydroxide; 9 c.c. of acetone are added and the precipitate centrifuged. The supernatant liquid is adjusted to a pH of 5.9 with 66 per cent sulfosalicylic acid. If a precipitate is formed, it is discarded; 1 c.c. of Sörensen's phosphate buffer is added to the liquid plus 18 c.c. of acetone and stirred and centrifuged for ten minutes. The supernatant fluid is withdrawn and the viscous precipitated layer contains the pregnancy reducing and gonadotropic factors. These are dissolved in 5 c.c. of water and 1 c.c. is treated with a few drops of 5 per cent starch solution and heated in the water bath at 38° C. until starch iodine color remains. In a total of 303 cases there were 108 correct positives and 80 correct negatives. The percentage of accuracy is 98.4 per cent. It is believed that the use of this reducing factor is a valid basis for a chemical test for pregnancy.

W. B. SERBIN.

Kraus, Anny, and Koenigstein, Rudolf: Experiences With the Pregnancy Test of Kapeller-Adler Histidinuria in Pregnant Women, *Chinese M. J.* 59: 129, 1941.

The positive histidine test during pregnancy, though not specific, must be considered a very important sign for the diagnosis of pregnancy. Morning specimens of urine give the best results.

C. O. MALAND.

Effkemann, G., and Werle, E.: Significance of Diminished Histaminase Activity of the Blood in Pregnancy in Initiating Abortion, *Zentralbl. f. Gynäk.* 64: 221, 1940.

The authors report an increase in the histamine-storing ability of the blood to 10 times normal by the sixth to eighth month of pregnancy as a result of increase in histaminase. A large amount of histaminase is found in the maternal blood and circulating through the placental tissues. The significance of the release of extra histamine into the circulation lies in its effect on tissue permeability. Outside of the inactivating effect of histaminase in pregnancy other substances prevent the full contraction-stimulating effect of histamine on the uterus.

In cases of abortion, the authors found the maternal blood and serum were able to take up much more histamine than in normal pregnancy, regardless of the type of abortion, indicating a much lower blood-histamine content in this condition. In cases of habitual abortion, the authors believe, there is a constitutional adrenal

cortex defect involving the failure to influence adequate histaminase storage, as well as corpus luteum and vitamin E insufficiencies. Blood histaminase values return to normal in a few days after the death of the ovum in early pregnancy as effect of the disappearance of placental histaminase. It should be remembered, however, that histaminase activity is also decreased in normal pregnancy with coincident infection, which may perhaps explain the occurrence of abortion or premature labor in these cases. The author suggests the administration of histaminase in threatened or habitual abortion.

R. J. WEISSMAN.

Cope, C. L.: The Diagnostic Value of Pregnanediol Excretion in Pregnancy Disorders, Brit. M. J. 2: 545, 1940.

Pregnanediol, produced by corpus luteal and placental activity, is present in the urine only in the luteal phase of normal menstruation and during pregnancy. On this premise the author studied over 100 cases of pregnancy, some 75 of which were seriously abnormal, in an effort to evaluate pregnanediol analysis as a diagnostic aid in obstetric disorders.

After discussing the normal behavior of pregnanediol and the means of estimating its secretion, the author summarizes his findings as to the value of pregnanediol in obstetric diagnosis.

Pregnancy is the only known condition in which amenorrhea is associated with the continued excretion of pregnanediol; hence this test is of importance in the diagnosis of early pregnancy. Consequently, the absence of pregnanediol in the urine in the case of amenorrhea usually means the absence of pregnancy. In both cases 2 or more tests must be made to be of significance. In a woman with signs and symptoms of a threatened abortion if pregnanediol is persistently absent in 2 or more determinations, 1 of 3 conditions is suggested, an inevitable, incomplete, or a missed abortion. The clinical findings must be considered to distinguish between these 3 possibilities. The presence of such serious abnormalities can often be detected by tests for pregnanediol when classical signs and symptoms are absent or have not yet appeared. In cases of suspected intrauterine death, pregnanediol determinations may give a clue to the diagnosis or strengthen or confirm a suspicion of the diagnosis.

The author warns that certain factors may affect pregnanediol excretion and lead to a misdiagnosis. These include such conditions as chronic nephritis and toxemias of pregnancy.

In considering the relative merits of the Aschheim-Zondek and pregnanediol excretion tests in the diagnosis of pregnancy disorders, there are advantages, technical, to each. However, as to the comparative value of each test no study has as yet been made.

FRED L. ADAIR AND H. W. PHILLIPS.

Kelso, Rich E.: A Twenty-Four-Hour Test (Aschheim-Zondek Modification) for the Diagnosis of Pregnancy, Am. J. Clin. Path. 10: 293, 1940.

Kelso points out that the employment of rabbits in the Friedman test has certain disadvantages: they are more expensive than mice, more difficult to breed, they have to be isolated for thirty days prior to use, and a small percentage of them do not respond to pregnancy urine hormone. In order to achieve greater economy and convenience and a more rapid diagnosis, the author developed a modified test in which rats are employed and which requires only twenty-four hours for its completion.

The test consists of using four immature female rats between twenty-two and forty days old. Two of the rats are injected with 1 c.c. of the urine at 9 A.M., 1 P.M., and 5 P.M. on one day, and are killed and examined at 9 A.M. the next morning. The two other rats are injected with 0.5 c.c. of the urine at the same intervals on two successive days, and the animals are killed and examined on the

fourth day, that is, seventy-two hours after the first injection. These latter tests are performed primarily for control purposes.

A total of 130 urine specimens including cases of normal pregnancies, ectopic pregnancies, missed and threatened abortions, endocrine dyscrasias, etc., were tested. In five instances the twenty-four-hour test showed a positive reaction, while the seventy-two-hour test was negative. Clinically these patients were eventually shown not to be pregnant. In 125 cases there was perfect correlation between the twenty-four- and the seventy-two-hour tests. The author concludes therefore, that this new twenty-four-hour test on rats is superior to any previously described and fulfills the requisites of a reliable and rapid pregnancy test.

J. P. GREENHILL.

Daniel, S. P., and Tien, B. S.: *The Significance of Pregnanediol in Pregnancy Urine*, Chinese M. J. 59: 416, 1941.

The excretion of sodium pregnanediol glucuronidate in the pregnancy urine of Chinese women at various stages of gestation agrees with that in Western countries. In a case of twin pregnancy, definitely higher values of pregnanediol were encountered throughout the whole course of gestation. The yield of pregnanediol with isobutyl alcohol as the extracting solvent was found to be only 64 per cent of that with normal butyl alcohol. From the data they have accumulated so far they consider that it is still premature to regard the excretion of sodium pregnanediol glucuronidate in the urine of pregnant women as an accurate index in the metabolic process of the corpus luteum hormone.

C. O. MALAND.

Paddock, Richard: *A Test for Pregnancy*, South. M. J. 34: 174, 1941.

The author has originated a biologic test for pregnancy which is based upon certain changes in the external genitalia of the guinea pig. The vagina of this test animal is occluded by a membrane which is absent for about forty-eight hours during the estrous period, which has a fifteen- to seventeen-day cycle. Injection of estrogenic substances, or the serum of pregnant women causes a disappearance of the vaginal closure membrane. Three thirty- to forty-five-day-old female guinea pigs with closed vaginal membranes are used, and 1.2 to 1.5 c.c. of blood serum is injected subcutaneously into the pectoral region of each animal. The test is read at the end of forty-eight hours and the interpretations are as follows: (a) Positive for pregnancy, if the vagina in each animal is partly open or wide open; if two show patency while the third is closed; (b) negative for pregnancy, if all three, or two of the animals have closed vaginas. Evidence of marked congestion of the genitals or only suggestive signs may be seen. If vaginal patency occurs in two of the three animals between forty-eight and seventy-two hours the test should be repeated. After a one- to two-day interval, the guinea pigs may be used again.

A total of 254 pregnancy tests were performed by the author employing 28 animals; thus an average of 9 tests per animal was obtained. The largest number of times that any pig was used was ninety-five.

The results of this test compared favorably with those obtained with a modified Friedman test routinely employed in the same clinic. The few erroneous results were toward the negative, and there were no known false positive reactions.

Simplicity and economy are the advantages claimed by the author for this biologic test. It is not difficult to learn the changes that occur in the genitalia, and, only a small number of test animals need be maintained.

ARNOLD GOLDBERGER.

Henriksen, Erle: *Pregnancy Tests of the Past and the Present*, West. J. Surg. 49: 567, 1941.

The author presents a rather complete, precise and at the same time highly amusing summary of practically all known pregnancy tests in a short paper, the

larger part of it taken up by excellent, cartoonlike, descriptive illustrations, beautifully drawn by Ted Bloodhart of the Department of Medical Art.

Henriksen's concluding statements read as follows: In reviewing the methods offered from time to time we have been impressed by the ingenuity of the empirical tests devised for the diagnosis of pregnancy. The Egyptians, 3,300 years ago, recorded pertinent observations upon the urine of gravid females indicating the presence of a substance capable of inducing the germination of seeds, an action similar to that characteristic of current biologic tests. As it is with many of the other so-called modern suggestions, we must admit the truth of the proposition formulated by Aristotle, "probably all art and all wisdom often have already been fully explored and again quite forgotten." Notwithstanding the progress of medical knowledge, an infallible diagnosis is still awaited more hopefully today than ever before. Thus, as it has been down through the ages, the question remains, "Is she pregnant? (see Fig. 10)."

HUGO EHRENFEST.

Weisman, Abner L., and Coates, Christopher W.: The Frog Test (*Xenopus laevis*) as a Rapid Diagnostic Test for Early Pregnancy, *Endocrinology* 20: 141, 1941.

Xenopus laevis is the South African clawed toad.

The authors list the investigators in this field, all of whom established the diagnosis of pregnancy after injecting the *Xenopus laevis* with concentrates of APL derived from urine. The technique consisted of injecting 1 c.c. of a simple alcohol or acetone extract of the suspected urine into the dorsal lymph space of from 5 to 12 animals. The extrusion of hundreds of macroscopic eggs six to eighteen hours after injection was considered a positive reaction. Apparently, the results of 600 collected tests were in agreement with Aschheim-Zondek test 99 per cent of the time.

The authors then report the results of their own investigative work on 12 imported *Xenopus laevis*. The 12 animals were divided, 2 each in 6 tanks designated as A, B, C, D, E, and F. The animals in A received 1 c.c. of sterile water. The animals in the other tanks were given standardized commercial APL (Parke-Davis antuitrin-S) in varying doses as follows: Tank B, 10 R.U.; Tank C, 50 R.U.; Tank D, 100 R.U.; Tank E, 250 R.U.; Tank F, 500 R.U. All medications were given by subcutaneous injection into the dorsal lymph space. The animals were observed eighteen hours after injection.

Animals in Tanks A, B, and C showed no reaction, in Tanks D and E, marked positive reactions and in Tank F, both animals died. The results of similar experiments repeated in the New York Aquarium are mentioned and corroborate the above findings.

The authors conclude that it is unlikely that the large amount of anterior pituitary-like hormone necessary to produce ovulation in the *Xenopus laevis* could be found in the normal pregnancy urine.

CLAUDE J. EHRENBURG.

Gelle, P., and Driessens, J.: Biochemical Changes of the Blood During the Course of Pregnancy, *Presse méd.* 48: 861, 1940.

The writers performed biochemic studies upon 45 pregnant women. Twenty-five of them were at term while the remaining two groups, in first and second trimesters, each included 10 pregnant women.

The biochemic observations obtained from each of these cases included the plasma and blood chlorides, blood sugars, blood ureas, blood proteins, blood polypeptides, the total nonprotein nitrogen of the blood, evaluation of the serum and globulin fractions of the blood proteins, electrometric determination of the blood pH and the determination of the alkaline reserve.

The authors found no gross disturbances of the biochemic equilibrium of the blood during the course of the pregnancy. Mild variations did occur. These changes

were found essentially in the plasma and blood chlorides, the pH of the blood and in the alkaline reserve. Mild deviations of the nonprotein blood constituents were also noted. From the physicochemical viewpoint gestation is accompanied by a well-compensated but moderate acidosis.

The investigators conclude that the biochemic approach offers insufficiently significant blood chemistry changes to warrant further exploitation of biochemic blood studies to explain the pathogenesis of toxemias of pregnancy.

CLAIR E. FOLSOME.

Cadden, J. F.: *The Glutathione Content of Blood During the Puerperium*, J. Lab. & Clin. Med. 23: 1266, 1938.

Glutathione is distributed throughout the body in blood and muscle. A study was made of the blood glutathione in a series of 40 cases during labor and the puerperium. The blood was drawn early in labor and immediately following delivery. In addition, determinations in 20 patients were made on the first, third, fifth, seventh, and ninth days of the puerperium; in the remaining 20, on the second, fourth, sixth, eighth, and tenth days of the puerperium. It was found that during labor, blood glutathione increased from an average of 35.9 mg. per 100 c.c. in early labor to 39 mg. immediately following delivery. Following delivery, there is a decrease during the first three days of the puerperium, probably due to blood loss during delivery. From the third to the eighth post-partum days, there is a rapid rise in glutathione, due probably to the formation of new red blood cells which have a higher glutathione content. Between the eighth and tenth days of the puerperium, the concentration of glutathione in the blood maintains a level approximately 18 per cent higher than that noted during labor.

W. B. SERBIN.

Horwitz, O., and Farley, D. L.: *Vitamin B Deficiency in Pregnancy as Indicated by a Test for OBT Principle*, Surg. Gynec. & Obst. 71: 313, 1940.

Numerous articles have appeared indicating that a deficiency of vitamin B₁ occurs frequently in pregnancy and that this deficiency may be overcome by administration of the vitamin. The symptoms of this deficiency have been reported as polyneuritis, hyperemesis gravidarum, numbness and tingling of the fingers and toes, tenderness of the extremities to pressure, muscular weakness, loss of deep reflexes, anorexia, periodic nausea, glossitis, tachycardia, edema, easily induced fatigue, etc.

Thirteen pregnant women, from a total of 100, studied by a test on blood serum, were found to be low in vitamin B₁ titer.

The OBT level, details of the test described in a previous article, can be raised by the administration of yeast over a four-day period.

Patients judged to be low in vitamin B₁ by this test have a definite tendency to develop neuritic symptoms.

One patient who developed eclampsia, had an adequate titer of OBT.

From this study it would appear that a deficiency of vitamin B₁ in pregnancy has a definite effect upon the appetite.

WILLIAM C. HENSKE.

Ribeiro, Daniel: *Vitamin C in Pregnancy*, Rev. de gynec. e. d'obst. (Rio de Janeiro) 2: 107, 1940.

This paper summarizes the principal studies and the role which vitamin C plays during pregnancy. The author reports thirty cases of pregnant women on whom he made tests for vitamin C saturation and shows, in conclusion, that all the observations made in the thirty cases showed deficiency in vitamin C.

MARIO A. CASTALLO.

Brieger, Hubertus: Vitamin C Metabolism in Pregnancy, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 80, 1940.

This report is from the department of Physiology at Rostock, headed by Wachholder who has done considerable work with vitamin C. The study was carried out to attempt to determine what happens to vitamin C metabolism in pregnancy under varying conditions of intake. The guinea pig, rat, and rabbit were used. Reports are given on only small numbers of animals and techniques are not described. The results, however, are of considerable interest.

Wachholder and his associates have shown that in both young and old animals, a diet low in vitamin C gives rise to an inability to stabilize oxygen consumption although in older rats this may ultimately be stabilized at a level above the normal. In young growing animals developmental disturbances occur. In general, similar changes occur in the rat, the guinea pig, and the rabbit.

Moriquand reported that the guinea pig on a scorbutic diet remained free of evidence of vitamin C deficiency during the second half of pregnancy but showed such evidence after delivery. The statement is made that the rabbit shows similar findings. Neuweiler, on the other hand, was unable to confirm this and stated that signs of scurvy appeared in the pregnant guinea pig just as quickly as in the non-pregnant. It is this disagreement which Brieger is attempting to settle.

Brieger's observations are based on animals obtaining a diet deficient in vitamin C but containing some.

A superimposed graph of the oxygen consumption per gram minute over a period of nine days in three guinea pigs is shown. The pregnant deficient animal showed the most regular oxygen consumption at about normal level. The pregnant animal on full diet showed considerable variation about this level while gross variations appeared in the nonpregnant deficient animal as evidence of an inability to stabilize oxygen consumption.

Experiments were carried out to determine in vitro the ability of various tissues to produce vitamin C under different conditions. In the guinea pig which was pregnant and had been on a green diet, no significant tissue synthesis could be demonstrated. Tissues of both pregnant and nonpregnant guinea pigs who had been on deficient but not vitamin C free diets showed significant increases in vitamin C content after six hours in normal saline at 37° C. The tissues from the pregnant animals showed a constantly greater increase than those of the nonpregnant. The greatest increase was found in the last part of pregnancy and here all maternal organs apparently synthesized vitamin C. The maternal portion of the guinea pig placenta showed an increase in vitamin C after six hours. The fetus can synthesize little vitamin C.

It is concluded that a protective mechanism is produced in pregnancy in these animals on varying degrees of vitamin C dietary deficiencies. It is to be presumed that the human being acts somewhat similarly. Decrease in tissue vitamin C levels should not at once be considered to be evidence of an avitaminosis in view of the stability of the oxygen consumption in the pregnant deficient animal. Saturation deficits in pregnancy should not be translated at once into terms of deficient intake although this does not mean that an increased intake during pregnancy is not desirable. On the contrary, lower levels of vitamin C in the fetus are demonstrated for the guinea pig when the intake is deficient. The synthesis of vitamin C can protect the mother but not the fetus from scurvy. As well, the deficient mother can develop scurvy quickly under these conditions after delivery.

The questions posed by a study of vitamin C in many obstetric and gynecologic problems are of such interest and probable importance that such information as is available should serve to stimulate work on the subject even though, as in this report, the results do not yet approach finality.

J. L. McKELVEY.

Gaetgens, G.: Nutrition During Pregnancy in the Light of Present Day Food Rationing, *Med. Klin.* 36: 561, 1940.

An investigation of the food requirements of pregnant women leads Gaetgens to maintain that during gestation a woman weighing 60 kg. (132 pounds) requires

between 2,500 and 3,000 calories daily. She should have between 90 and 100 Gm. of protein, 60 Gm. of fat and between 400 and 500 Gm. of carbohydrate. The intake of table salt should not exceed 5 Gm. a day. The vitamin content should consist of 80 to 100 mg. of vitamin C, 10,000 international units of vitamin A, and 1,500 units of vitamin B.

J. P. GREENHILL.

Stieve, H.: Exit of Intervillous Blood from the Human Placenta, *Zentralbl. f. Gynäk.* 64: 1570, 1940.

In a well-documented and illustrated report, the author demonstrates the communication between maternal veins and placental intervillous spaces in all parts of the uterine surface of the placenta, in contrast to the idea of a limited, special marginal zone, postulated by some writers, where blood was able to enter the maternal venous system. The appearance of valvelike structures and sphincters in these veins indicates the functioning of some sort of a regulatory mechanism.

R. J. WEISSMAN.

Kropp, Benjamin: The Content and Distribution of Minerals in Human Amnion and Chorion at Term, *Anat. Rec.* 77: 407, 1940.

The method used by the author was that of microincineration. Both the placental and nonplacental portions of the amnion and chorion were studied. It was found that the cytoplasm of the nonplacental part of the amnion is rich and the nuclei are poor in minerals. The quantity of water soluble minerals, including calcium is low in the cytoplasm. In the placental portion of the amnion, most of the minerals are present just within the cell membrane, except at the base of the cell which is invariably ash free. The basement membrane of the amnion is a mineral-free structure. A small amount of mineral, probably silica, is present in the epithelium of both amnion and chorion. The decidua and connective cells are rich in water-soluble minerals and contain more iron than either the amniotic or chorionic epithelium.

WILLIAM BERMAN.

Becker, R. F., Barth, E. E., and Schulz, M. D.: Fetal Swallowing, Gastro-Intestinal Activity and Defecation in Amnio, *Surg. Gynec. & Obst.* 70: 603, 1940.

That amniotic fluid may be swallowed by the fetus and that it may serve some nutritive function in the growth process during intrauterine existence is not a new idea.

Under normal physiologic conditions in utero, the guinea pig fetus begins to swallow amniotic fluid about the forty-second day of gestation. This fact is indicated by the presence of a stomach shadow in roentgenograms after the amniotic sac has been injected with 0.4 to 1.0 c.c. of colloidal thorium hydroxide or dioxide (thorad or thorotrast).

The rapidity with which the thorium reaches the fetal stomach after injection and the efficiency with which the material is propagated along the gastrointestinal tract increases with age.

Late in fetal life, usually not before the sixtieth day, defecation begins to occur in amnio as a normal phenomenon. Meconophagy is also a normal physiologic function of guinea pigs in utero. The cycle of swallowing, defecation, and reswallowing of the thorium-impregnated meconium may be repeated several times before birth.

It has been suggested, but proof is lacking, that the swallowing of the amniotic fluid is important from the standpoint of prenatal water metabolism. It may be significant that swallowing begins when the fetus is just starting to grow at its most rapid rate. Comparison with conditions in the rabbit suggests the probability that at this point the efficiency of the fluid exchange from the placenta via the blood stream is declining and that the fetus makes use of its reserve of fluid in the amniotic sac.

WILLIAM C. HENSKE.

Dietrich, Doris: The Variation of Duration of Pregnancy in Brood Animals and Its Cause, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 296, 1940.

This reports a study of the literature dealing with the duration of pregnancy in various large domestic animals. Its object is to obtain information which will aid in the critical evaluation of prolonged human pregnancies. It is recognized that there is a gross difference in controlling the details of duration of pregnancy in the human being and in the lower animals. In the animal isolation is possible and coitus during heat makes a clearly defined beginning. In the human being, the last menstrual period may have little relation to the next ovulation and histories may be unreliable. The legal German maximum duration of pregnancy for the human being is set at 302 days post coitum.

The literature dealing with the horse, donkey, and cow is summarized. There apparently is no adequate veterinary observation to determine the development of the newborn animals in relation to variations in duration until gross postmaturity with fetal dystocia is reached. But it is interesting that the curves for variation in duration of pregnancy in the horse and in the woman are almost exactly the same. The variation in duration in the animals included in the study is of an order to support the concept that human pregnancy might continue for 302 days after coitus. In the horse the extremes are 280 and 370 days. The short duration probably means nothing but the upper extreme is almost 40 days beyond the average of 331 days. It should be noted, however, that the chance of pregnancy in the horse lasting beyond 365 days is only 0.2 per cent. The vast majority of pregnancies last between 320 and 345 days in the horse.

Similar variations are reported to occur in the other animals mentioned.

A consideration of the causes of variation in duration of pregnancy in these animals leaves little which can be directly carried over to the human being. It can be readily demonstrated in animals that there is a species variation. Pregnancy in the mare mated with the donkey is longer than that in the mare mated with the male horse. Variations of pregnancy duration in various species of horses and cows are listed. Species can be made to change the pregnancy duration by the addition of other species' genes to the strain. Average duration is less in multiple pregnancies but this obviously brings in other factors. The average duration is slightly longer ($1\frac{1}{2}$ to 3 days) when the fetus is a male. Poor general physical condition seems to prolong pregnancy. Seasonal variations occur and may be related to available nourishment and exercise. Age of the animal may be a factor.

No original material is presented but the report contains a useful summary of literature which is not readily available. An adequate bibliography is attached.

J. L. McKELVEY.

Tscherne, E., and Engelhart, E.: New Viewpoints on the Question of Prolonged Pregnancy, *München. med. Wchnschr.* 87: 996, 1940.

In discussing the subject of prolonged pregnancy Tscherne and Engelhart feel that several points should be considered carefully, viz., (1) the length of the menstrual cycle, since the usual calculation of the delivery date is based on the twenty-eight-day cycle; (2) if the delivery date is ten days or more after the correctly determined date, the danger to the baby increases, especially in older primiparas. In a series of 1,222 cases the mortality figures varied from 7 to 19 per cent; (3) that the great danger to the baby should make us watch these patients carefully, not to wait too long before using operative measures and to consider induction of labor in time and, in the presence of complications, to consider cesarean section; (4) to verify the diagnosis of prolonged pregnancy through the objective information offered by determining with x-ray the proximal epiphyseal center of the tibia. If this diameter is near 7 mm., a prolonged pregnancy is very probable.

The authors also discuss the theory that the cause of the prolongation is a disturbed relationship between the placenta follicular hormone and the corpus luteum hormone, which theory seems to be strengthened by the fact that the hormone assay of the placenta in these cases shows subnormal values of follicle hormone.

C. E. PROSHEK.

Hosemann, H.: The Law Concerning Duration of Pregnancy, München. med. Wchnschr. 87: 715, 1940.

Hosemann studied the records and statistics of the largest obstetric clinics in various countries and concluded that the application of the old Rule of Naegele to determine the duration of pregnancy is still the most practical. The only change necessary to get better results is to modify this rule for those large groups of women in whom the cycle may be longer or shorter than twenty-eight days. In these cases the author suggests that the number of days that differ from the twenty-eight-day cycle be added to or subtracted as the case may be.

C. E. PROSHEK.

Cruikshank, Lewis G.: Leucorrhea in Pregnancy; A Study of 200 Cases, J. Obst. & Gynaec. Brit. Emp. 47: 109, 1940.

In this study the author has attempted to correlate the cause of leucorrhea by means of the relative proportion between epithelial cells and leucocytes, the character of the bacterial flora, the hydrogen-ion concentration of the vaginal contents, and the state of the vaginal epithelium in respect to glycogen deposition. The types were divided into Type I, a pure Döderlein flora; Type II, Döderlein bacilli mixed with a fair sprinkling of smaller gram-positive bacilli with perhaps one or two gram-negative bacilli; Type III, a mixed flora consisting of a great variety and number of organisms, chiefly small gram-positive and gram-negative cocco-bacilli. Spirochetes, comma bacilli, and leptothrix were searched for. The presence or absence of *Trichomonas vaginalis* or the hyphal filaments or blastospores of the parasite of vaginal thrush were specially looked for. In the cervical smear the relative proportion between mucus and epithelial cells and pus cells was noted and a diligent search for gonococci was made.

Two-hundred pregnant women supposed to be suffering from leucorrhea were examined. Twenty per cent showed a normal vaginal flora. Cervical lesions including erosions were found in nearly 40 per cent of the cases. In more than half of these, however, there were other causes of leucorrhea. Gonorrhea accounted for four cases among the two hundred. The parasite of vaginal thrush was found to be the cause of the leucorrhea in 25 per cent of the cases. The *Trichomonas vaginalis* parasite was found in 40 per cent of the cases and was found to be the most common offender. Eight cases were unclassified. In general, the recovery was associated with a change in the bacterial flora, and a return of the pH to between 4 and 5.

WILLIAM BERMAN.

Items

American Congress on Obstetrics and Gynecology

Special Notice

The committee which is sponsoring the next American Congress on Obstetrics and Gynecology, to be held in St. Louis on April 6 to 10, 1942, represents the only organization outside of governmental bodies which has attempted to unite the efforts of voluntary and other agencies to carry out the widely disseminated plans for the care of women and children and believes that in this time of stress, there should be a definite interest in the welfare of the mothers and babies of the nation. Opportunity for the presentation of advances in obstetric and gynecologic knowledge will be afforded to the many groups interested in these problems at a nationwide gathering of this kind. The Directors of the project believe that, notwithstanding the war situation, the Congress should be held at the stated time and are proceeding with their plans to make of this an outstanding gathering. Further details of the program will be communicated as these are made available. Inquiries may be addressed to the Central Office, 650 Rush Street, Chicago, Illinois.

Notes on the preliminary program will appear in the March issue of the JOURNAL.

Postgraduate Courses in Obstetrics at Chicago Lying-in Hospital

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of \$25.00 is required on registration, \$10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

The general oral and pathologic examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Wednesday, June 3, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942. It will greatly facilitate the work of the Board if applications are filed as far as possible in advance of the closing date for their receipt.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Rules Governing the Award of "The Foundation Prize," American Association of Obstetricians, Gynecologists and Abdominal Surgeons

1. The award which shall be known as "The Foundation Prize" shall consist of \$150.00.

2. Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

3. Manuscripts must be presented under a *nom de plume*, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the *nom de plume* and containing a card showing the name and address of the contestant.

4. Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

5. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the *Journal of the Author's choice*. Unsuccessful contributions will be returned promptly to their authors.

6. Three copies of all manuscripts and illustrations entered in a given year must be in the hands of the Secretary before June 1.

7. The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

8. The President of the Association shall annually appoint a Committee on Award, which, under its own regulations shall determine the successful contestant and shall inform the Secretary (James R. Bloss, 418 Eleventh Street, Huntington, W. Va.) of his name and address at least two weeks before the annual meeting.

Books Received

PREECLAMPTIC AND ECLAMPTIC TOXEMIA OF PREGNANCY. By Lewis Dexter, M.D., Research Fellow in Medicine, Harvard Medical School, and Soma Weiss, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard University, etc. In collaboration with Florence W. Haynes, Herbert S. Sise and James V. Warren. 415 pages with 44 illustrations. Little, Brown and Co., Boston, 1941.

MOTHER AND BABY CARE IN PICTURES. By Louise Zabriskie, R.N., Director, Maternity Consultations Service, New York City, etc. Second edition, revised and reset. 208 pages with 204 illustrations. J. B. Lippincott Company, Philadelphia, 1941.

OBSERVACIONES SOBRE LA CLINICA DEL PUERPERIO. Por Carlos Alexander Ruelas. Universidad Nacional Autonoma de Mexico, Facultad de Medicina. Editorial Cultura, Mexico, D. F., 1941.

DISEASES OF WOMEN. By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology, Washington University School of Medicine, etc., and Robert James Crossen, Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Ninth edition, entirely revised and reset. 948 pages with 1127 engravings, including 45 in color. The C. V. Mosby Company, St. Louis, 1941.

GYNECOLOGY AND FEMALE ENDOCRINOLOGY. By Emil Novak, Associate in Gynecology, the Johns Hopkins Medical School, etc. 605 pages with 425 illustrations, many in color. Little, Brown and Company, Boston, 1941.

THE BLOOD BANK AND THE TECHNIQUE AND THERAPEUTICS OF TRANSFUSIONS. By Robert A. Kilduffe, Director, Laboratories, Atlantic City Hospital, etc., and Michael DeBakey, Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana, etc. 558 pages with 214 illustrations and one color plate. The C. V. Mosby Company, St. Louis, 1942.

SEMIOLOGIA DO OVÁRIO, com um estudo particular da citologia vaginal. Par Dr. Francisco Victor Rodrigues, Professor de Clinica Ginecologica da Faculdade Fluminense de Medicina da Universidade do Brasil, etc. Casa do Livro Limitada, Rio de Janeiro, 1941.

I'M GONNA BE A FATHER. By Bob Dunn. Illustrated. David McKay Company, Philadelphia, 1941.

OUR SEX LIFE. A Guide and Counsellor for Everyone. By Fritz Kahn. Second, revised edition. 459 pages. Illustrated. Alfred A. Knopf, New York, 1942.

HERNIA. By Alfred H. Jason, Consulting Surgeon, Long Beach Hospital, etc. 1325 pages with 355 illustrations. P. Blakiston Company, Philadelphia, 1941.

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American Journal of Obstetrics and Gynecology

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No. 3

Central Association of Obstetricians and Gynecologists

Thirteenth Annual Meeting, October 2 to 4, 1941

THE RELATION OF INHALATION ANALGESIA AND ANESTHESIA TO ASPHYXIA NEONATORUM*

CURTIS J. LUND, M.S., M.D., MADISON, WIS.

*(From the Department of Obstetrics and Gynecology, University of Wisconsin, and
the State of Wisconsin General Hospital)*

FREEDOM from asphyxia neonatorum should constitute one of the important properties of an ideal obstetric inhalation analgesic or anesthetic agent. Nevertheless, we must recognize that this is but one of the necessary and desirable qualities. Guedel¹ has defined an ideal anesthetic agent for obstetrics as one that "should have no ill effect, immediate or remote, upon either the mother or the baby. It should render true physical relief from suffering, and should be applicable over a long period of time without influence upon uterine contraction. It must present to the obstetrician a patient in satisfactory condition for correct delivery, and to be practical it must admit of convenient and simple application."

It would be presumptuous for an obstetrician to speak with authority concerning the physiology, pharmacology, and clinical management of obstetric anesthesia. The converse would be equally as true. Yet there is an intermediate zone in which the knowledge and experiences of both must be integrated, and it is on this common ground that we must meet while discussing this material. The subject must be limited to the

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

Aided by a grant from the Wisconsin Alumni Research Foundation, Madison, Wis.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

relationship of various inhalation agents to asphyxia neonatorum rather than a general consideration of obstetric inhalation agents.

Notwithstanding the voluminous literature concerning obstetric anesthesia there is a paucity of actual data about its influence on asphyxia neonatorum. Many of the older reports dismissed the subject with a general statement or two without attempting to study its many ramifications. Recent investigators have begun an attack on the problem in a systematic manner.

Cole and others,² Henderson and collaborators,³ and Heard⁴ are of the opinion that ether or some of its combinations, when used as obstetric anesthetic agents, definitely increase asphyxia neonatorum, while Embree⁵ found little asphyxia definitely attributable to either ether or chloroform. Nitrous oxide and cyclopropane were both superior to ether, in Heard's estimation, but he obtained the least asphyxia neonatorum following spinal anesthesia for cesarean section. Much has been written about nitrous oxide and asphyxia neonatorum, particularly during the past few years when the full significance of its relation to oxygen deficiency was appreciated. Davis⁶ and Clifford and Irving⁷ noted that nitrous oxide may be given for long periods of time without significant effect on the newborn infant. Plass and Swanson⁸ in a comparative study of ethylene and nitrous oxide in obstetrics stated that there was a greater incidence of asphyxia neonatorum following the use of nitrous oxide. The increase, however, was in the mild type of asphyxia. Very little statistical material has appeared regarding cyclopropane. After studying a small series of cases, Smith⁹ was of the opinion that the agent was very readily and quickly transmitted to the infant. He was not prepared to state any definite conclusions as to its value in obstetrics.

MATERIALS AND METHODS

As a part of a general survey of the etiologic factors of asphyxia neonatorum, the department of anesthesia generously cooperated by permitting the use of their detailed records of anesthesia. These were

TABLE I. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE* ASPHYXIA
Respiratory	Onset respiration	Spontaneous Immediate	Spontaneous oligopnea 1-5 min.	Delayed apnea 5-15 min.	Delayed apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous Lusty	Delayed Vigorous Lusty	Delayed Weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous Active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

*All infants alive at onset of labor but who died during labor are included in this group.

combined with the obstetric data and then recorded by the punch-card method. A complete record of 1,982 deliveries was obtained. All of the deliveries were in this hospital and were immediately supervised by trained resident obstetricians and anesthetists or by permanent staff members, a fact which lends uniformity and accuracy to the records. Table I shows the classification of asphyxia neonatorum used for this study. The use of the punch-card system necessitates accurate definitions of the conditions to be recorded. Usually the criteria have varied according to the personal views of the particular investigator, and therefore we have adhered to the classification which has proved satisfactory in our experience. It is unfortunate that so many exist. Occasionally incomplete records may have led to minor errors in classification of the mild types of asphyxia, but in the "moderate" and "severe" groups the data have been uniform. Because of the necessity for brevity and clarity, the "moderate" and "severe" forms will occasionally be combined into a single unit called "dangerous" asphyxia which will differentiate it from the "mild" group.

In a previous publication,¹⁰ it was observed that prematurity, complications of pregnancy and labor, methods of delivery, and misuse of analgesics were some of the more important causes of asphyxia neonatorum. Each of these factors must be considered in any investigation of inhalation agents.

Because of the variation in detail of treatment of each case, it is difficult to determine the contribution of inhalation agents to the incidence of asphyxia neonatorum. In general, however, the following methods were used. In the majority of uncomplicated term pregnancies, the individual received moderate amounts of nonvolatile analgesic drugs, usually opiates, during the early part of the first stage of labor. Later in the first stage and during the second stage of labor nitrous oxide was commonly used as an inhalation analgesic, and it was given intermittently with contractions by a semiclosed technique. Nitrous oxide, cyclopropane, and ethylene were used at the time of delivery in concentrations such as to produce surgical anesthesia as opposed to analgesia. Nitrous oxide and ethylene were used for some simple operative procedures. At the present time the less potent agents such as nitrous oxide and ethylene are rarely used for operative deliveries, instead cyclopropane and occasionally ether or chloroform are given. Ether and chloroform were chiefly used when conditions demanded complete relaxation for operative obstetrics or in cases of emergency when other equipment was unavailable.

The judicious management of the patient thus gives rise to so many variables that the results require circumspect analysis. In spite of these many variables certain interesting and significant facts appear.

RESULTS

The total cases have been divided into six groups according to the type of inhalation agents received (Table II). In the nitrous oxide

TABLE II. ASPHYXIA NEONATORUM IN RELATION TO INHALATION AGENTS

AGENT	NO. CASES	NO ASPHYXIA PER CENT	MILD ASPHYXIA PER CENT	MODERATE ASPHYXIA PER CENT	SEVERE ASPHYXIA PER CENT
Nitrous oxide	1,115	89.0	6.0	4.0	1.0
Nitrous oxide and ethylene	133	85.0	8.5	3.0	3.5
Nitrous oxide and cyclopropane	319	83.5	7.5	7.0	2.0
Cyclopropane	181	67.5	9.5	17.0	6.0
Others	69	76.5	4.5	12.0	7.5
None	165	84.5	7.0	6.0	2.0
Grand total	1,982	85.0	6.8	6.0	2.2

group are placed all patients receiving that agent alone, usually as an analgesic agent. Two other groups received nitrous oxide as an analgesic agent, but it was supplemented either by ethylene or by cyclopropane as anesthetic agents for delivery. A fourth group had no preliminary analgesia and the patients were anesthetized with cyclopropane. This group embraced a series of complicated cases which, for the most part, were delivered operatively either vaginally or by cesarean section. The fifth group designated "others" was made up of patients receiving ether, chloroform, and an occasional local or spinal anesthesia. This group was small and heterogeneous and of little statistical significance. The final group were those having no inhalation agents, frequently not by choice but because of other factors, including precipitate delivery.

TABLE III. INHALATION AGENTS AND TYPE OF DELIVERY

AGENT	SPONTANEOUS				OPERATIVE			
	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE
N ₂ O	997	90.0	6.0	4.0	118	79.0	7.5	13.5
N ₂ O	36	91.5	5.3	3.0	97	82.5	9.5	8.0
C ₂ H ₄								
N ₂ O	111	88.5	7.0	4.5	208	81.0	7.5	11.5
C ₂ H ₆								
C ₂ H ₆	22	91.0	0.0	9.0	159	63.5	10.5	26.0
Others	27	89.0	7.0	4.0	41	68.0	2.5	29.0
None	165	86.0	6.0	8.0				
	LOW FORCEPS				OTHER VAGINAL OPERATIONS			
	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE	NUMBER CASES	NONE PER CENT	MILD PER CENT	MODERATE AND SEVERE
N ₂ O	85	79.0	8.0	13.0	33	79.0	3.0	18.0
N ₂ O	67	83.5	7.5	9.0	17	88.0	6.0	6.0
C ₂ H ₄								
N ₂ O	162	84.0	7.0	9.0	44	70.5	9.0	20.5
C ₂ H ₆								
C ₂ H ₆	20	70.0	5.0	25.0	17	66.5	8.5	25.0
Others	10	80.0	0.0	20.0	20	50.0	5.0	45.0

Method of Delivery.—An analysis of similar methods of delivery with each of the several agents indicate that the given procedure is more significant in the production of asphyxia than is the anesthetic agent. For example (Table III) all spontaneous deliveries show about the same amount of moderate and severe asphyxia neonatorum, approximately 4 per cent, whether the analgesic agent was nitrous oxide, ethylene, cyclopropane, or others.

Low forceps delivery was used only upon definite clinical indications. It thus differs somewhat from the outlet or prophylactic forceps delivery which is in common use. In this group, it is interesting to note that the best results were obtained when nitrous oxide was used as a preliminary analgesic agent and ethylene or cyclopropane used as the anesthetic agent for delivery. When nitrous oxide alone was used for forceps delivery, the incidence of fetal asphyxia was higher, probably because the concentration of nitrous oxide necessary for surgical anesthesia gives rise to fetal anoxia.

A comparison of all operative deliveries gives the same general results except for the apparent paradox in the two groups of patients that received cyclopropane for anesthesia. In one group anesthesia was preceded by nitrous oxide analgesia while the patient was bearing down with her contractions; in the other group, the patient was immediately anesthetized with cyclopropane and delivery consummated. The latter group included most of the cesarean sections, a method of delivery atraumatic to the fetus. The nitrous oxide-cyclopropane group all had vaginal operative delivery with its attendant trauma to the fetus. Subsequent data will give some information about this discrepancy.

Type of Delivery and Premedication.—By minimizing the influence of nonvolatile analgesics and trauma of delivery, both etiologically significant factors in asphyxia neonatorum, it is possible to gain some definite data about the inhalation analgesic agents. It can be seen (Fig. 1) that in unpremedicated spontaneous deliveries asphyxia neonatorum is at a minimum regardless of the type of inhalation agent employed. Some of the groups contained so few cases that they have little statistical value, but the results, such as they are, tend to support the conclusions drawn from the larger series. These are that the type of delivery and premedication are more significant in asphyxia neonatorum than is the type of inhalation agent. One other point should be considered, this again concerns the two cyclopropane groups. In the unpremedicated operative series the incidence of dangerous asphyxia for the two cyclopropane groups is similar and relatively low. However, following premedication, the incidence increases. This study is being extended to cesarean section where apparently similar results are being analyzed.

Prematurity.—It has been previously shown¹⁰ that prematurity is one of the outstanding factors in any study of asphyxia neonatorum. The question that immediately arises is: Are prematures more sensitive to a certain inhalation agent, to all inhalation agents, or to none? Because of the rather limited number of premature deliveries (approximately 15 for each agent in each of the seventh and eighth months of pregnancy),

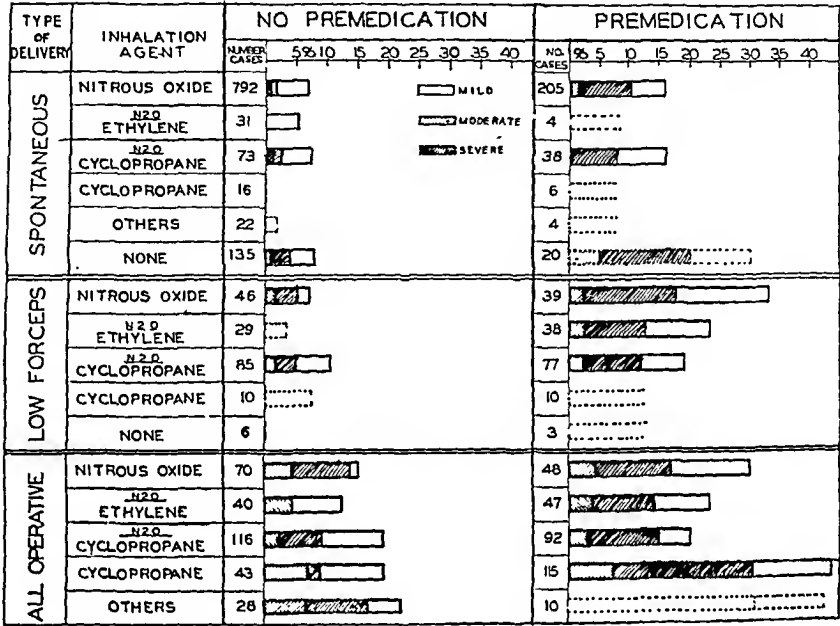


Fig. 1.—Chart showing that with various agents there is little difference in incidence of asphyxia neonatorum when the cases are separated according to delivery and premedication.

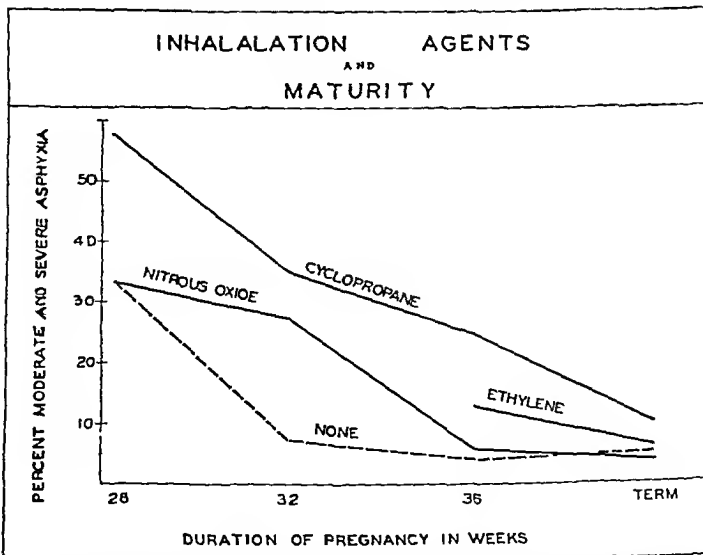


Fig. 2.—The very young prematures have asphyxia regardless of agents. By thirty-two weeks those having no inhalation agents were less susceptible to asphyxia. At thirty-six weeks all agents but cyclopropane were well tolerated by the infant. At term all agents were similar in effect on asphyxia neonatorum.

the results are not conclusive. However, the indications are that, at the twenty-eighth week of gestation, the inherent fragility of the fetus offsets any effects of the inhalation agents. At the thirty-second week those infants having no inhalation agents were definitely superior to others. But, by the thirty-sixth week this sensitivity was no longer demonstrable except for cyclopropane. At term there was little difference; however, the more potent agent cyclopropane still gave evidence of greater asphyxia (Fig. 2).

Complications of Pregnancy.—The unusually large number of cases presenting some type of complication of pregnancy or labor made it possible to demonstrate the marked effect that they have on neonatal asphyxia. In many instances it was not the complications per se that

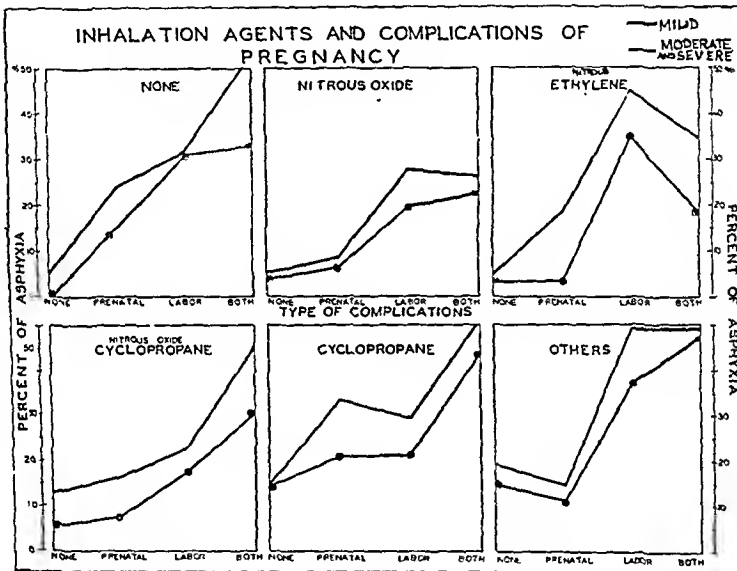


Fig. 3.—Complications of prenatal period and of labor are more significant in the production of asphyxia than are the inhalation agents. The incidence of "mild" and "dangerous" asphyxia neonatorum under each of these conditions is evident.

were responsible for the asphyxia but their influence on the conduct of labor. Among 728 complicated cases and 1,251 uncomplicated ones, dangerous asphyxia was three times as common in the former group. For comparative purposes these two groups were subdivided into four: (1) patients with no complications, (2) those showing prenatal complications only, (3) patients with complications during labor only, and finally (4) those having both prenatal complications and complications of labor. In Group 1 the combined moderate and severe asphyxia neonatorum was 5 per cent; in Group 2, 10 per cent; in Group 3, 20 per cent; and in Group 4, 30 per cent. As can be seen (Fig. 3), the mild type of asphyxia is remarkably constant under all conditions, a fact which has been repeatedly observed in all of our analyses. This has raised the question as to the significance of that class; perhaps it

is an inherent accompaniment of labor that would be unavoidably present under all circumstances. The influence of complications on asphyxia neonatorum can be seen at a glance. Further analysis of those uncomplicated cases show that there is little dangerous asphyxia in the groups receiving no agents, nitrous oxide or ethylene. There is some increase in the group receiving cyclopropane or "other" agents. This may be due in part to the agents. Most of these patients had operative delivery and that would add another factor.

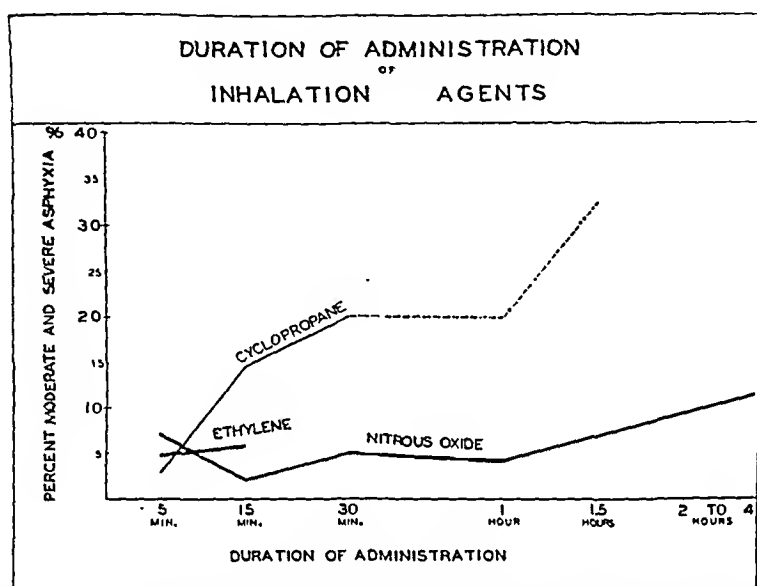


Fig. 4.—Prolonged administration of cyclopropane quickly increases the incidence of asphyxia. Nitrous oxide may be given for long periods of time with little increase in asphyxia neonatorum.

Duration of Administration of Agents.—There seems to be a striking difference in the effects of various agents on the fetus when administered for varying periods of time. Because of this difference each agent must be analyzed singly. Nitrous oxide administration was followed by increased asphyxia only when given for very short or for very long periods of time (Fig. 4). The short periods of administration were usually associated with rapidly progressing labors with tumultuous pains and delivery imminent. Increasing the concentration of nitrous oxide at this point in order to obtain pain relief or to prevent delivery reduced the oxygen content of the blood reaching the fetus, with resulting asphyxia. This particular point was repeatedly verified by observing slowing of the fetal heart rate as oxygen want intervened. This increase in asphyxia, coincident with prolonged administration, may or may not have been the fault of the gas. There is an increase in incidence of asphyxia neonatorum with prolongation of the second stage of labor beyond one and one-half hours, and this rather than the nitrous oxide was probably the etiologic factor. In a group

of 50 cases without prolongation of the second stage of labor, nitrous oxide was given from three to twelve hours with little increase of "dangerous" asphyxia.

Ethylene was not given for long periods of time but these data would indicate that it was slightly superior to nitrous oxide when given for five minutes but slightly inferior when given for fifteen minutes. Cyclopropane was in distinct contrast to the other agents. With it neonatal asphyxia was at its minimum when administration was limited to five minutes; in fact, at this time interval it surpassed the other agents under consideration. Asphyxia increased rapidly as the time of administration increased. After fifteen minutes the "moderate" and "severe" asphyxia had increased from 3.5 to 14 per cent and at the end of thirty minutes' administration it was 20 per cent.

Technique of Administration.—Anesthetic techniques do not ordinarily concern the obstetrician, so they will not be discussed at length. There was no correlation between technique of administration and asphyxia neonatorum. The following data about nitrous oxide are typical of results we have obtained: Semiclosed technique (with some rebreathing), 971 cases with 6 per cent "dangerous" asphyxia; closed absorption technique, 94 cases with 6.5 per cent; and McKesson technique, 466 cases with 7 per cent asphyxia.

Others.—Numerous other correlations have been made, yet none of them add significant details to this study. In passing, however, two of them should be mentioned. The first is that of parity. As would be expected, there was greater incidence of asphyxia in the first born than in those of subsequent pregnancies, but this was unrelated to the inhalation agents used. It is interesting to note that there were 610 multiparas having nitrous oxide as the sole analgesic agent. In this group there was but 1.0 per cent "severe" asphyxia, and 1.5 per cent moderate asphyxia, or a total of 2.5 per cent of "dangerous" asphyxia.

Further studies were made to correlate the duration of the first and second stages of labor. Again there was no significant relation to inhalation agents. When the first stage of labor was prolonged beyond thirty to thirty-six hours, there was an increase in incidence of asphyxia neonatorum regardless of the agent used at termination of labor. Likewise, when the second stage was longer than one and one-half or two hours, there was an increase in asphyxia neonatorum irrespective of the inhalation agents used.

DISCUSSION

Nitrous oxide.—Like most of the analgesic and anesthetic agents, nitrous oxide has had its periods of popularity and decline. The early literature was summarized by Davis¹¹ in 1916. Since that time nitrous oxide has been in general use. Eastman's observations¹² that dangerous

fetal oxygen want existed when nitrous oxide was given to the mother in concentrations of 90 per cent or more have caused many to discard the agent. This is an unfortunate occurrence. The average trained anesthetist will in most cases have little difficulty in giving nitrous oxide analgesia without significant fetal oxygen want. Furthermore, even the less expert anesthetist may be reasonably well assured that no dangerous fetal oxygen want exists as long as the fetal heart rate remains within normal limits. Our results indicate that nitrous oxide may be given for long periods of time as an analgesic agent without danger. When asphyxia neonatorum occurs after use of nitrous oxide, the agent has been used incorrectly, without sufficient oxygen, for some procedure requiring a more appropriate agent.

Ethylene.—This agent has had extensive use in the midwest as an analgesic and anesthetic agent. From the point of view of asphyxia neonatorum, our studies would indicate that it was as satisfactory as nitrous oxide for purposes of analgesia. In this series it was used as an anesthetic agent only for some simple operative procedures in which it was superior to nitrous oxide and compared favorably with cyclopropane. Our observations would indicate that with proper regard for oxygen concentrations ethylene may be given for analgesia and limited anesthesia without significant effect on the incidence of asphyxia neonatorum.

Cyclopropane.—This agent is a relative newcomer to the field of obstetric analgesia and anesthesia. Little more than opinions have been expressed in the literature. In this series of 500 administrations, the following conclusions seem warranted. As an analgesic agent cyclopropane compares favorably with nitrous oxide and ethylene in the incidence of asphyxia neonatorum. As an agent for general anesthesia, it causes some increase in the incidence of fetal asphyxia but probably no more than any other anesthetic agent. When used as an agent for general anesthesia, asphyxia neonatorum varied directly with the duration of the administration of cyclopropane. Induction is very rapid with this agent, permitting the anesthetist to have the patient anesthetized in a short time. If the obstetrician proceeds without unnecessary delay, most deliveries may be completed before the cyclopropane has had time to depress the respiratory function of the infant. In this manner the qualities of the agent may be properly utilized.

Others.—From the few cases in this group, it is hazardous to draw any definite conclusions. There are indications that, as with previous agents, general anesthesia causes some increase in asphyxia neonatorum.

SUMMARY

1982 consecutive deliveries were reviewed from the aspect of asphyxia neonatorum in relation to inhalation analgesic and anesthetic agents.

1. Nitrous oxide, ethylene, and cyclopropane, when used as analgesic agents, did not materially influence the incidence of asphyxia neonatorum.
2. Nitrous oxide, properly administered, was given for long periods of time without significant effects on fetal asphyxia.
3. Cyclopropane and other agents when used in concentrations sufficient for anesthesia by operative delivery were accompanied by an increase in the incidence of fetal asphyxia.
4. The incidence of asphyxia neonatorum varied directly as the duration of administration of cyclopropane anesthesia.
5. There seemed to be no relationship between asphyxia neonatorum and the type of anesthetic technique.
6. Prematurity, complications of pregnancy and labor, method of delivery and misuse of analgesic agents were apparently of greater significance in asphyxia neonatorum than the various inhalation agents when properly administered.

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DISCUSSION

DR. RHETT McMAHON, BATON ROUGE, LA.—The essayist has certainly presented an extraordinary series of cases and his conclusions are so well backed up by facts that they offer little opportunity for discussion. However, I feel that all anesthetic agents do influence the production of anoxemia. Even nitrous oxide if prolonged will produce asphyxia, mild in degree at first, but when pushed to the stage of anesthesia, the asphyxia increases. Our experience with ethylene was so unsatisfactory on account of several dangerous cases of asphyxia that it is not used in our service at all. With nitrous oxide we have had more experience, and it is our choice for analgesia.

The time element is so important, especially when doing cesarean section, that we now have our patient completely prepared before the administration of our anesthesia. In that way we reduce the amount used and feel we have reduced the asphyxia.

The body of this paper clearly proves one of the author's opening statements, namely, that we have no ideal obstetric analgesic procedure. We are often stampeded into the injudicious use of these agents by lay pressure. It is incumbent upon meetings like this fully to inform the public of the status of these problems.

Patients should be told that in spite of what *Time Magazine*, *Life* and the *Ladies' Home Journal* say, we have no ideal obstetric analgesia, that there is no such thing as a safe, painless delivery, and that many children are being sacrificed today because this is not fully appreciated.

DR. JAMES R. MANLEY, DULUTH, MINN.—We have some trouble every once in a while with general anesthetics in forceps delivery, principally because the patients are not prepared for anesthesia. They have been given something to eat and the stomach is full, when the doctor decides to apply forceps. These patients have difficulty with cyanosis and vomiting. I wonder if the baby is not asphyxiated if the mother is cyanotic for five or ten minutes during the delivery.

I saw one case recently in consultation. The patient had been cyanotic for a while, and aspiration of the trachea was necessary. The baby was born dead, but the autopsy showed no injury and the fetal heart had been all right during the early part of the anesthesia. Does Dr. Lund believe that such cyanosis in the mother contributes to asphyxia in the baby?

DR. JOHN F. KELLY, INDIANAPOLIS, IND.—I would like to put in a word for local anesthesia as I have used it in a considerable number of cases after having been first forced to its use in a patient with heart failure some years ago. Lately I have been using it less perhaps because a patient has to be watched closely in order to start the local nerve block procedure at the proper time.

Most of my experience has been with pudendal block and an occasional experience with parasacral block. The resident at the Coleman Hospital ran a series of 50 cases last year using a method of sacral block. He introduced a ureteral catheter into the sacral canal and left it there until the perineal stage, so that at any time the novocain solution could be injected. Technically I found this difficult but it worked well in the hands of this resident.

Local anesthesia can be used very satisfactorily on private patients and the baby breathes spontaneously as if nothing were used to relieve pain. Pudendal block can sometimes be started within two hours of an instillation of rectal ether and the patient remembers nothing of the performance. If the pudendal block is not sufficient for outlet forceps, it at least reduces the amount of general anesthesia to a very few minutes and the episiotomy can be repaired without anything else.

DR. LUND (closing).—As to Dr. McMahon's question I think there is no doubt that gas by itself may have some effect on asphyxia neonatorum. In this series of cases we had no opportunity to study normal cases without gas analgesia so our study would add little in this respect to our previous knowledge.

One point that I want to bring out is the excellent quality of anesthetists which we have in our institution. This is the answer to many of our problems, and this is why we have had such good results in many of these cases.

As to Dr. Manley's question, I have made the same observation; namely, in a baby which died in utero following a period of extreme maternal cyanosis. If there is maternal cyanosis we can usually expect asphyxia of the infant. When maternal cyanosis occurs in the course of delivery I think it well to postpone delivery until the cyanosis has been cleared up. Undoubtedly trauma of delivery in the presence of oxygen want adds to the hazard, so for that reason it is better, I believe, to correct the maternal oxygen want and then proceed with the delivery.

We have had little experience with local anesthesia. Dr. Henderson's presentation before this Society last year discussed that problem very satisfactorily.

RADIUM IN THE TREATMENT OF UTERINE BLEEDING CAUSED BY BENIGN LESIONS*

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Mayo Foundation)*

COMPLETE follow-up records were studied on 196 women who experienced atypical uterine bleeding (menorrhagia and/or metrorrhagia) caused by benign conditions, five or more years after treatment by radium or roentgen rays. These treatments were administered by the section on therapeutic radiology of the Mayo Clinic. Our results are given on the basis of satisfactory control of the bleeding, and for the younger women we have considered also the preservation of menstrual and reproductive function. In all cases treatment was preceded by dilatation and curettage and microscopic examination of the endometrium removed.

Atypical uterine bleeding frequently occurs in the first half of the reproductive life of women. In these cases the initial treatment should always aim to regulate and preserve the menstrual function. Such methods of treatment are known to all and need not be enlarged on in this paper. In certain cases all conservative forms of treatment fail and more radical measures must be adopted as a means of preserving the health or saving the life of the patient. When conservative methods of treatment fail and no evidence of pathologic change of the pelvic viscera can be found, small amounts of radium may be applied in the uterine cavity. A considerable experience with doses of from 150 to 300 mc. hours for women less than thirty years of age has shown a fair percentage of success. Not infrequently menstruation has become fairly regular in amount and interval and some patients have borne children thereafter. If this form of treatment should fail, hysterectomy can be performed subsequently. Stacy and Mussey¹ previously have discussed this group of patients.

Although it is not possible to draw an arbitrary age limit, it is frequently more difficult to regulate gross abnormalities of menstruation by conservative measures after the age of thirty years. After this age, myomatous changes in the uterus become more common and may interfere with the results of conservative treatment. The end results of old pelvic inflammatory disease begin to occur and the function of the ovaries begins to wane. Nevertheless, until the age of forty years is

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, October 2 to 4, 1941.

reached, physicians are reluctant to inhibit ovarian function permanently unless this measure is necessary to preserve the health of the individual. For patients between thirty and forty years of age, an attempt is often made to achieve control of atypical uterine bleeding by a submenopausal dose of radium. This procedure is used particularly for patients in the early part of the fourth decade of life. In the latter part of this decade more and more patients are given a menopausal dose when radium is used. When increased amounts of radium are employed, temporary or permanent inhibition of function of the ovaries will occur more frequently. When the usual general symptoms of the menopause do appear and require treatment with estrogenic substances after irradiation therapy, often the chance of recurrence of atypical uterine bleeding which then may require further treatment is increased. Furthermore, the younger the ovary the greater its recuperative capacity. Consequently a certain percentage of women less than forty years of age who receive a calculated menopausal dose of radium will subsequently have spontaneous recurrence of atypical uterine bleeding which may necessitate further treatment.

REVIEW OF LITERATURE

The literature contains many contributions in which the relative merits of surgical and radiation treatment of this condition are debated. Ward² suggested 1,800 mg. hours for patients more than forty years of age. Corseaden³ in a recent report used from 600 to 2,400 mg. hours for patients less than thirty-eight years, and 3,000 mg. hours for patients more than thirty-eight years when associated fibroids had enlarged the uterus to the size of two and one-half months of pregnancy. Brown and his associates⁴ employed dosages of roentgen rays from 125 to 1,000 r. They felt that it takes 625 to 749 r. to assure permanent cessation of menstrual function. Corseaden expressed the belief that 300 r. anteriorly and 300 r. posteriorly will cause amenorrhea for a period of six to eight months in the case of women less than thirty years of age but that the same dosage may cause permanent amenorrhea among women more than thirty-eight years, and that 600 r. will sterilize most women. In their study the initial doses of radium ranged from 250 mg. hours to 1,200+ mg. hours. The dose employed for most women at or near the menopause was 1,200 mg. hours.

Keene and Payne⁵ studied 423 cases of functional uterine bleeding. After tabulating the results of radium used to control the bleeding in 391 cases, they came to the conclusion that in at least 50 per cent some other form of treatment was required. They reported one death for which the treatment could not be held responsible. Their mortality rate following hysterectomy was 0.5 per cent. They stated that surgical treatment with conservation of ovarian tissue will be followed by severe menopausal symptoms in 7 per cent of cases. In their experience, treatment with radium of women thirty years of age or less resulted in restoration of menstruation to normal in 88 per cent of cases; permanent amenorrhea occurred in 6 per cent and severe menopausal symptoms in 8 per cent. Of forty married women in this group, 5 gave birth to normal babies and 8 had miscarriages after irradiation. For patients between thirty and forty years of age the picture changed. Bleeding of 95 per cent was

controlled; 24 per cent had permanent amenorrhea and 21 per cent severe menopausal symptoms. With initial doses of 200 to 300 mg. hours of radium, the bleeding of 80 per cent was controlled without permanent amenorrhea or severe menopausal symptoms. When 800 to 1,200 mg. hours of radium were given, permanent amenorrhea occurred in 56 per cent and severe menopausal symptoms in 47 per cent. In this group, 10 pregnancies occurred among 70 patients which resulted in 6 normal babies and 4 miscarriages. With a dose of 1,200 mg. hours, the bleeding of women aged forty to fifty years was controlled in 97 per cent of cases but severe menopausal symptoms occurred in 38 per cent. In their experience radium therapy approached perfection when the patients were between the ages of fifty and sixty years.

Norris and Behney⁶ found in 1,437 cases of hemorrhage from the uterus caused by benign conditions that in 750 cases bleeding was due to functional causes and in 687 cases myomas were present. Satisfactory results were obtained in 83 per cent by the use of radium; in 3 per cent bleeding recurred in ten years or more. Carcinoma developed after irradiation in 1.09 per cent. About the same proportion of satisfactory results were obtained in cases in which myomas were present as in cases of functional hemorrhage. The mortality rate in the entire group was 0.278 per cent.

Rousseau⁷ reported the findings in 841 cases of uterine bleeding caused by functional conditions, the menopause, or fibroids. He came to the conclusion that fibroids contributed to the bleeding in more than 50 per cent of cases. He stated that in 5 per cent of cases in which treatment with radium was employed operation may be required later, and in 95 per cent satisfactory results should be obtained from radium.

On the other hand Heaney,⁸ Gough,⁹ Suggs,¹⁰ Schlink,¹¹ Squire and Allen,¹² and others have favored hysterectomy to a menopausal dose of radium or roentgen rays, especially for women less than forty years of age, and have stated that in most instances elective operation is less radical than irradiation.

Corscaden recently reported a series of 733 cases of atypical uterine bleeding that occurred with or without uterine myomas; these cases had been traced for an average of eight years. The bleeding was controlled with radium or roentgen rays in 719 (98.1 per cent) and uncontrolled in 14 (1.9 per cent). Supplementary irradiation was required in 30 (6.1 per cent) of 493 cases in which radium was employed and in 18 (7.6 per cent) of 240 cases in which roentgen treatment was given. Corscaden expressed the belief that the chief cause of failure in these cases was submucous myomas.

RESULTS OF STUDY OF CASES

Since the gynecologist or general surgeon is most often confronted with the question of irradiation or operation for those women who are forty years of age or less we have divided our series of 196 patients into two main groups: (1) those forty years or less of age and (2) those more than forty years of age.

The results of varying doses of radium on 79 patients forty years of age or less who did not have demonstrable myomas at the time of the initial examination or at the time of the dilatation and curettage are given in Table I. Of 79 patients, 47 (59.4 per cent) experienced satisfactory results from the initial dose of radium. An additional 10 pa-

TABLE I. RESULTS OF VARYING DOSES OF RADIUM ON PATIENTS FORTY YEARS OF AGE OR LESS WITHOUT MYOMAS

	DOSE, MG. HR.			TOTAL
	LESS THAN 500	500-1000	1000-1200 OR MORE	
Patients	20	29	30	79
Results				
Satisfactory	8	17	22	47
Unsatisfactory	12	12	8	32
Additional radium	2	3	5	10
Hysterectomy	6	5	1	12
Dilatation and curettage			1	1
Removal of ovarian tumor			1	1
No additional radium or operation; continued trouble	4	4	0	8

tients (13.5 per cent) were given subsequent radium treatments with good results. Twelve patients (15.1 per cent) required hysterectomy before the bleeding was controlled. Eight patients (10.1 per cent) had severe menopausal symptoms. Four pregnancies occurred among the 64 married women (6.2 per cent). Of 35 patients forty years of age or less who had myomas, 15 (42.8 per cent) obtained satisfactory results following the initial dose of radium (Table II). One patient had

TABLE II. RESULTS OF VARYING DOSES OF RADIUM ON PATIENTS FORTY YEARS OF AGE OR LESS WITH MYOMAS

	DOSE, MG. HR.			TOTAL
	LESS THAN 500	500-1000	1000-1200 OR MORE	
Patients	10	16	9	35
Results				
Satisfactory	2	8	5	15
Unsatisfactory	8	8	4	20
Additional radium	1	0	0	1
Hysterectomy	6	8	3	17
No additional radium or operation; continued trouble	1	0	1	2

a subsequent application of radium. Hysterectomy was subsequently performed on 17 patients (48.5 per cent) who had myomas which contributed to the bleeding. Four patients (11.4 per cent) in this group complained of severe menopausal symptoms. Of the 30 married women, only one became pregnant after treatment.

Forty-seven patients more than forty years of age were treated with radium (Table III). This includes those who had uterine fibroids and

TABLE III. RESULTS OF RADIUM ON PATIENTS MORE THAN FORTY YEARS OF AGE WITH AND WITHOUT MYOMAS

	DOSE: 1000-1200 OR MORE MG. HR.*	
	NO MYOMAS	MYOMAS
Patients	27	20
Results		
Satisfactory	25	18
Unsatisfactory	2	2
Hysterectomy	1	2
No additional radium or operation; continued trouble	1 death	

*Additional radium was not given in any case.

those who did not have them. All of these patients received doses of radium of 1,000 mg. hours or more. Of the 27 patients who did not have myomas, 92.6 per cent received satisfactory results. Four patients in this group (14.8 per cent) had severe menopausal symptoms. One patient in this group died of a pulmonary embolus on the fourteenth day after dilatation and curettage and insertion of radium into the uterus. Of 20 patients who had myomas, 90 per cent received satisfactory results. One patient (5 per cent) had severe menopausal symptoms.

The results of abdominal and vaginal applications of radium to 14 patients in both age groups are given in Table IV. In only 2 cases in

TABLE IV. RESULTS OF ABDOMINAL AND VAGINAL RADIUM ON PATIENTS IN BOTH AGE GROUPS

	AVERAGE DOSE	
	PATIENTS 40 YR. OF AGE OR LESS	PATIENTS MORE THAN 40 YR. OF AGE
	ABDOMINAL 12,000 MG. HR.	VAGINAL 800 MG. HR.
Patients	11	3
Results		
Satisfactory	9	1
Unsatisfactory	2	2
Additional radium	0	1
Hysterectomy	1	1 (Dilatation and curettage)
No additional radium or operation; continued trouble	1	0

the combined group was a diagnosis of uterine myoma made. This number was so small that these cases are classed with those in which no myomas were demonstrable. Ten (71.4 per cent) obtained satisfactory results. Two patients experienced severe menopausal symptoms, and one pregnancy occurred among the 12 married women.

In 21 cases of functional uterine bleeding roentgen therapy was employed (Table V). Even with the smaller doses the results in this

TABLE V. RESULTS FOLLOWING ROENTGEN THERAPY

	DOSAGE, ROENTGENS*				
	PATIENTS MORE THAN 40 YR. OF AGE			PATIENTS 40 YR. OF AGE OR LESS	
	700	960	1680	525-960	1242-1760
Patients	1	4	3	7	6
Results					
Satisfactory	1	4	3	6	5
Unsatisfactory	0	0	0	1	1
Additional roentgen treatment	0	0	0	0	1
Hysterectomy	0	0	0	1	0
No additional roentgen treatment or operation; continued trouble	0	0	0	0	0

*The dosage listed represents the total roentgen dosage. The number of fields varied per patient.

group were excellent. The results in 19 of the 21 cases (90.4 per cent) were satisfactory. The bleeding of all of the patients who were more than forty years of age was controlled with the initial dose of roentgen rays. Among the patients forty years of age or less one required further

roentgen therapy and one patient had a hysterectomy. There were no deaths following roentgen therapy.

We were particularly interested in what happened to the group of patients who were forty years of age or less. These cases were divided according to age and dose of radium received (Table VI).

TABLE VI. RESULTS OF RADIUM TREATMENT OF ALL PATIENTS FORTY YEARS OF AGE OR LESS

	DOSAGE, MG. HR.				
	AGES 36-40		AGES 27-35		TOTAL
	1,000 OR LESS	MORE THAN 1,000	1,000 OR LESS	MORE THAN 1,000	
Patients	37	38	38	12	125
Results					
Satisfactory	20	27	17	7	71
Unsatisfactory	17	11	21	5	54
Additional radium or x-ray	2	4	3	2	11
Hysterectomy	10	5	15	2	32
No additional radium or operation; continued trouble	5	2	3	1	11

Of the patients from thirty-six to forty years of age, inclusive, 62.7 per cent obtained satisfactory results. The bleeding of 20, or 54 per cent, of the patients in this age group who received 1,000 mg. or less hours and that of 27, or 71 per cent, of the patients in this age group who received more than 1,000 mg. hours was controlled. Of the patients aged from twenty-seven to thirty-five years inclusive approximately, 50 per cent obtained satisfactory results. The bleeding of 44.7 per cent of the patients in this age group who received 1,000 mg. hours or less of radium and that of 58.3 per cent of those who received 1,000 mg. hours or more was controlled. Of 125 patients forty years of age or less, 21 (16.8 per cent) menstruated regularly after radium therapy. The other patients in this group of 125 had either permanent amenorrhea or an occasional scanty flow.

The pregnancies of 106 married women following radiation for functional uterine bleeding are listed in Table VII. Pregnancy did not occur in the group of cases in which roentgen treatment was given.

TABLE VII. RÉSUMÉ OF PREGNANCIES FOLLOWING TREATMENT WITH RADIUM*

AGE OF PATIENT YEARS	LABOR AND RESULT
36	Premature labor at 7 months; baby died
34	Patient died at time of delivery; baby apparently normal
37	Miscarriage early in pregnancy
35	Normal pregnancy
34	One year after radiation treatment miscarriage at 3 months
	One year later premature labor at 7 months; baby died
32	Five months pregnant at time of questionnaire

*The first two patients received 1,200 mg. hours and the last four 350 to 700 mg. hours of radium. None of these patients had myomas.

Of the 106 patients, 6 (5.6 per cent) had one or more pregnancies. Of these, 2 had miscarriages and 2 had premature labors and the babies did not survive. No information was obtained concerning fetal anomalies.

Malignant lesions developed in 2 cases after irradiation. In one total abdominal hysterectomy was performed for an early adenocarcinoma of the fundus of the uterus nine years after treatment with radium. In the other panhysterectomy was performed for a fibrosarcoma and adenocarcinoma of the uterus four years after roentgen therapy.

COMMENT AND SUMMARY

The results of radiation therapy in 196 patients who had atypical uterine bleeding not caused by a malignant condition were studied. One hundred and seventy-five patients were treated with radium and 21 with roentgen rays. The bleeding was satisfactorily controlled by the initial treatment in 134 (68.4 per cent). In 13 cases (6.6 per cent) subsequent radiation therapy was necessary before the bleeding was controlled. Thus good results were obtained in 147 (75 per cent). In 34 cases (17.7 per cent of the 196 cases) hysterectomy was performed sooner or later because of persistent bleeding. Eighteen patients (9.1 per cent) complained specifically of menopausal symptoms. Six pregnancies occurred among 106 married women, an incidence of 5.6 per cent.

There were 125 patients in this group who were forty years of age or younger and were treated with radium. Twenty-one (16.8 per cent) of these established a fairly normal menstrual cycle after radium therapy. One patient in the total group died from pulmonary embolism after dilatation and curettage and intrauterine application of radium.

The percentage of good results from all types of radium treatment increased with the age of the patients. Approximately 50 per cent of those aged twenty-seven to thirty-five years, inclusive, obtained good results from radium; 62.7 per cent of those thirty-five to forty years of age, inclusive, were satisfactorily treated, and 91.4 per cent of the patients more than forty years of age obtained satisfactory results. It is evident that as the age of the patients increased the dose of radium administered tended to increase. We believe, for patients more than forty years of age without fibroids or when fibroids are present but the uterus is not enlarged to more than its size after three months of pregnancy, that preliminary dilatation and curettage for diagnosis followed by intrauterine application of a menopausal dose of radium or the administration of roentgen ray therapy are excellent forms of treatment for atypical uterine bleeding. For the group of patients who are from thirty to forty years of age, the choice of treatment is made with more difficulty. To one who is surgically minded failure of about 25 per cent from radiation in the entire series would indicate that hysterectomy accompanied by a 98 to 99 per cent possibility of cure is preferable. By this method of treatment, it is possible to preserve the function of the ovaries and at least to delay the onset of the menopause. Further, surgical treatment will allow the correction of associated conditions that occur from relaxation of the pelvic supports as well as the removal of associated lesions.

The radiologist can point to a satisfactory control of bleeding in 75 per cent of cases at an initial risk of less than 1 per cent and the avoidance of a major surgical procedure. Radiation therapy does not preclude the subsequent performance of hysterectomy should it become necessary later.

Radium is often stated to be a conservative form of treatment. This may be true in the younger age group when 250 mg. hours or less is used or in the older women when an amount calculated to produce the menopause is used near or in the climacteric when ovarian function is shortly to cease. Radium or roentgen rays may be used in preference to surgical treatment for women in the fifth decade of life suffering from atypical uterine bleeding caused by benign lesions when the natural menopause is to be anticipated shortly, when a uterus is no larger than it is in the third month of pregnancy, when the operative risk is increased because of associated conditions and when no gross evidence of active pelvic inflammatory disease exists. We doubt whether radiation therapy is truly conservative in the fourth decade of life in the treatment of atypical uterine bleeding that has failed to respond to other treatment. It seems to us that sacrifice of a uterus whose function cannot be controlled and the preservation of the ovaries is more conservative. Naturally such a statement is made on the basis of a minimal mortality rate from hysterectomy.

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DISCUSSION

DR. EARL CONWAY SMITH, NEW ORLEANS, LA.—All cases of atypical uterine bleeding in the category of this series should have a *thorough* uterine curettage with microscopic examination of the tissues removed, as only by so doing can the occasional early malignancy be recognized and treated accordingly. Great emphasis should be placed upon the selection of the type of patient suitable for radium therapy. Radium should not be applied until all other more common measures have failed.

Not all will agree that radium should be used in puberal girls and women of the childbearing age due to the uncertain results which include the high incidence of miscarriages in the relatively rare pregnancies that do occur in those women that

remain fertile following its use. Through such reports we may learn to use even smaller doses of radium, thereby increasing the number who remain fertile after treatment.

Atypical bleeding in the first half of the reproductive life gives us our greatest worry when it cannot be controlled by conservative measures. Radium, when judiciously used with respect to proper selection of case and proper dosage, certainly has its field of usefulness here. The percentage of cures, even though the percentage of those establishing a regular menstrual rhythm is low after radium application, warrants its use in preference to hysterectomy, as hysterectomy can almost always be done later.

In the second half of the reproductive period (30 to 40 years), I believe the atypical bleeding cases of benign origin should be divided into two groups with respect to management. First, those patients extremely desirous of having a baby, and second, those who have their family or are known to be sterile. Both groups must, of course, be qualified by the presence or absence of definite indications or contraindications to surgery. In the first group, those desirous of becoming pregnant should be given a submenopausal dose of radium in the hope that ovarian function will be preserved. In the second group, I believe that total hysterectomy with conservation of ovarian function is the procedure of choice.

At the menopause, opinions are definite and favor the use of radium unless there are specific indications or contraindications for surgery.

Before radium is applied in any patient before the climacteric, a clear explanation should be made to that patient or to some responsible member of the family, that, although the bleeding is controlled in 60 to 90 per cent of the cases, nothing definite can be promised as to the preservation of ovarian function.

I, of course, condemn the use of radium in the fertile woman by the occasional operator.

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—In the group of younger women, in the absence of myomas or pathology of other kinds, we must assume that the bleeding of which the patient complains is in most instances due to some endocrine imbalance. When radium is used we know that further depletion of the function of the ovary, or interference with the normal function of the ovary occurs.

While the bleeding can be controlled by hysterectomy or radium, both of these methods are usually accompanied by an exaggeration of subjective symptoms. The dosage of radium has been found to be a very important factor not only in stopping the bleeding but in relieving the subjective symptoms. Nevertheless it is to be hoped that with increased knowledge of endocrine diagnosis and therapy, the need for radium and surgery in the absence of demonstrable pathology will be appreciably decreased.

DR. GILBERT F. DOUGLAS, BIRMINGHAM, ALA.—In a group of cases which we have been working on at the Hillman Hospital in Birmingham, we have, so far as possible, avoided both radium and x-ray. In treating these cases we endeavor to delay for a period of time and if necessary do several curettages before resorting to radiation. As a result, there have been very few of these cases that could not be corrected if proper study was done to determine the endocrine status of the subject. Certainly in the younger group we should work to determine if the condition cannot be corrected by more conservative means.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—In the past five years we have had at the Jefferson Davis Hospital more than 500 cases of uterine bleeding sent to us and in not one case have we used radium. Our experience with patients receiving radium from other sources before coming to us has been discouraging. I recall 3 patients with functional uterine bleeding sent to me who continued to

bleed after receiving radium and only stopped when they had received stilbestrol. There were also three patients who had been given the so-called stimulating dose of radium for bleeding due to benign lesions. The first two patients were told that their menstruation would stop for only a few months, but three years afterwards there still has been no sign of a flow. The other young girl had to have a laparotomy because of bleeding from the right ovary. The left ovary was found to be entirely atrophic and the right ovary was full of old clotted blood. Several private patients who have had large doses of radium for menopausal bleeding were also sent to me and were psychologic problems. Apparently I have seen only the bad side of radium therapy.

We have been giving 5.0 to 25.0 mg. of stilbestrol to stop uterine bleeding due to benign lesions. Our results have been most gratifying. We can keep these patients from bleeding for one month, six months, or twenty-four months. One young girl, age 19 years, was made amenorrheic for approximately 2 years. She has been closely watched and studied. Many blood chemistry studies and endometrial biopsies have been taken and none of these showed anything abnormal. She has now menstruated 6 times and the endometrial biopsies have all been pre-menstrual in morphology, which indicates that ovulation had occurred. She also had a laparotomy, and grossly there were no abnormal changes observed in the uterus and tubes. The ovaries were like those seen at a full-term pregnancy, that is, they were small, smooth, and devoid of normal follicular cysts.

According to our routine we give 5.0 to 25.0 mg. of stilbestrol in oil, according to the amount of bleeding, into the anterior lip of the cervix, using a spinal needle and a 10 c.c. syringe. If, however, the patient is not bleeding very much and is in good physical condition, she is given a prescription for twenty-five 5.0 mg. stilbestrol tablets and is instructed to take one tablet every night at bedtime for twenty nights. She has 5 extra 5.0 mg. stilbestrol tablets left, and these are to be used if needed for the withdrawal bleeding, because two to eight days following the taking of the last 5.0 mg. tablet she will spot for two or three days, bleed for two or three days, and then spot for two or three days more. If this bleeding is excessive she can take one or two of the 5.0 mg. stilbestrol tablets to check the flow. In 14 to 21 days later she will start to flow again. Eighty-seven per cent of the patients will flow normally again if thyroid is given up to tolerance (pulse of 100 to 110). To reach such a dose $\frac{1}{4}$ gr. is given every morning before breakfast, and every fourth morning the dose is increased $\frac{1}{4}$ gr. until the tolerance dose is reached, whether it be $\frac{1}{4}$ or 30 gr.

The more I study normal and abnormal uterine bleeding, the more I am convinced that bleeding is dependent on an estrogenic hormonal blood level. With an estrogenic blood level above or below this normal level the patient is amenorrheic. Examples are the amenorrhea of pregnancy, which is above the estrogenic bleeding, and the absent periods of the young girl before puberty, which is below the estrogenic bleeding level.

DR. WILLIS E. BROWN, OMAHA, NEB.—I should like to report the results of our experiences in the University of Nebraska and the University of Michigan with radiation therapy. In our studies we used a relatively new unit of measuring the amount of radiation delivered. The radiologists call this the "tissue roentgen." By this means they are able to compute the exact amount of radiation delivered to the ovary. We should not group our patients by so many milligram hours of radium or roentgens of x-ray for the effectiveness of this therapy will vary with the thickness, weight, and age of the patient.

It is our experience that 1,000 mg. hours of radium in a millimeter and one-half of platinum within the uterine cavity will only give you 75 per cent cessation of the uterine bleeding. If on the other hand we raise this by 300 or 500 mg. hours

for the heavy patients, the level of success will be increased to 95 per cent. The same thing is true of x-ray. If one can deliver 600 "tissue roentgens" to the ovary almost 100 per cent success will be obtained. Radiation therapy of this type is most suitable in patients who are 40 years of age or over. When the dosage is adjusted, the degree of success approximates that of surgical management.

DR. RANDALL (closing).—I made no attempt to discuss the endocrine therapy that might be used in these patients, inasmuch as they constitute a group in which endocrine therapy had failed and in which some more radical treatment was necessary. Furthermore these patients were treated in the period from 1930 to 1935 at a time when endocrine therapy was not as well advanced as it now is.

The point of the paper was to show what results were obtained by the doses of radium employed. I am particularly pleased at the discussion about the technique of the application of radium therapy. This applies especially to the patients over forty years of age. In the group under discussion, in many instances one tries to preserve menstrual function by using submenopausal or subcastration doses of radium. It seems to sum up to the fact that these patients should be intensively studied and treated with conservative measures first and later with radical measures if necessary. I do not believe we can make a flat rule as to treatment of this younger age group.

CLINICAL EVALUATION OF EQUINE GONADOTROPIN*

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GR^{EAT} clinical interest in the gonadotropic hormone from the serum of pregnant mares began with an excellent paper by Davis and Koff¹ in 1938, in which they claimed experimental ovulation in women for the first time. Thirty-six women at various stages of the menstrual cycle were given 50 to 70 units of "gonadogen" intravenously sixteen to seventy-six hours before operation. Sixteen patients had young corpora lutea. There was some skepticism of these results, but following the confirmation of Siegler² and others the production of ovulation in the normal or responsive ovary by this means is fairly generally accepted.

A number of papers have appeared since that time applying the hormone to clinical conditions. Unfortunately most of them have dealt with entirely clinical details in cases that might show spontaneous remissions, or with cases having such varied treatment as to leave doubt as to which may have been the effective therapeutic agent. It has seemed to us that sufficient groundwork has not been laid to advise complicated combinations of this hormone with others to obtain magic cures. Still other papers have been so enthusiastic as to be incredulous to a profession that has been so misled with chorionic gonadotropin.

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Two recent papers with well-studied cases are of interest because of their negative results.

Erving, Sears, and Roek³ (1940) concluded that 81 per cent of their 48 patients with sterility, dysfunctional flowing or amenorrhea were apparently unaffected by the mare's serum hormone. In no case was there any definite evidence of stimulation of ovulation. Vogt and Sexton⁴ (1941) reported 13 patients with amenorrhea and 4 with metrorrhagia. The patients with amenorrhea were primed with 16,000 units of estrone. Three with amenorrhea menstruated regularly and all 4 with metrorrhagia showed immediate improvement. No ovulatory effect on the endometrium was found in any case. A most important point in these two papers is that the prepared aqueous solution of the hormone (gonadin, Cutter) was used.

The present paper is intended to summarize our studies conducted over a period of three years on the dried form of this hormone (gonadogen, Upjohn). Our previously reported cases of patients with amenorrhea and metrorrhagia,⁵ (1940) and primary dysmenorrhea⁶ (1941) are resummarized here with a longer follow-up and additional cases. Also patients with male sterility are described, in an effort to bring together the main indications for the hormone at the present time, correlated with the results we have obtained. Throughout this work an effort has been made to use consistently the one hormone with no other therapy at the time, not because there may not be great value in combinations, but to determine any positive effects that the hormone alone may have. Thyroid has not been prescribed, although some patients would probably have been benefited by it. Clinical effects on bleeding, pain, and fertility have been noted and whenever possible endometrial biopsies or sperm counts have been obtained for objective data.

AMENORRHEA

Sixteen patients with secondary amenorrhea have been treated with the pregnant mare's serum hormone. Eleven had biopsies before treatment. Two had atrophic endometrium, 7 interval nonsecretory endometrium, and 2 endometrial hyperplasia (nonsecretory). Treatment was continued from one to nineteen months. Menstruation attributed to the hormone occurred in 12 patients. Two others menstruated three and fourteen months after treatment; in each instance the patient had received only one month's treatment. Two patients (Cases 1 and 3) were completely refractory after nine and twelve months of cyclic treatment, although one (Case 1) had one single menses after three months.

Of the 12 who had cyclic menstruation, 6 patients showed secretory endometrium (5 normal premenstrual) after treatment, while 4 had nonsecretory endometrium. But of those who had secretory endometrium, it is interesting that as treatment continued, the majority of menses were nonsecretory. Case 2 had two cycles of secretory and two cycles of nonsecretory endometria. Case 5 had three cycles of secretory and three cycles of nonsecretory endometria. Case 6 had

TABLE I. AMENORRHEA

CASE	AGE	DURATION	ENDOMETRIUM	P.M.S.* UNITS	OBSERVATION	CLINICAL RESULT	FOLLOW-UP BIOPSIES
1	18	3 yr.	Atrophic	400	36 mo.	One menses in 12 mo.	Nonsecret. 12 ×
2	19	6 mo.	Atrophic	260	36 mo.	Regular menses 2 yr.	Secretory 2 × Nonsecret. 2 ×
3	21	13 mo.	Nonsecretory	710	9 mo.	No menses	Nonsecret. 8 ×
4	24	9 mo.	Nonsecretory	100	6 mo.	Regular menses	
5	26	5 mo.	Nonsecretory	70	16 mo.	Regular menses	Secretory 3 × Nonsecret. 3 ×
6	23	14 mo.	Nonsecretory	930	38 mo.	Regular menses. No menses after treatment stopped	Secretory 3 × Nonsecret. 9 ×
7	23	10 mo.	Nonsecretory	120	6 mo.	Regular menses	Secretory 1 × Nonsecret. 1 ×
8	18	8 mo.	Hyperplasia	610	14 mo.	Regular menses	Nonsecret. or hyperplasia 10 ×
9	17	4 mo.		110	2 mo.	One menses	Nonsecret. 1 ×
10	25	8 mo.	Nonsecretory	30	17 mo.	No menses 13 mo. Then 3 menses	Nonsecret. 1 ×
11	28	20 mo.	Nonsecretory	40	5 mo.	One menses 3 mo. later	
12	19	13 mo.		610	23 mo.	Regular menses	Secretory 2 × Nonsecret. 9 ×
13	18	9 mo.	Hyperplasia	410	16 mo.	Regular menses	
14	26	6 mo.		240		Three menses followed by pregnancy	Secretory 1 ×
15	20	13 mo.		60	1 mo.	Menses in 14 days	
16	35	9 mo.		180	3 mo.	Regular menses	

*P.M.S., Pregnant mare's serum.

three cycles of secretory and nine cycles of nonsecretory endometria. Case 7 had one cycle each of secretory and nonsecretory endometria. Case 11 had two cycles of secretory and nine cycles of nonsecretory endometria. Case 14 had one cycle of secretory endometrium followed by a normal pregnancy and a normal child.

From these data it is evident that growth effects have occurred in the endometrium followed by secretory effects in six cases. Five patients are known to have continued cyclic menstruation over a period of months after the hormone was discontinued, and one is known to have stopped immediately after continuous treatment for twenty months. Even after ovulation apparently is established during treatment, it does not occur in the majority of cycles as treatment is continued. However these experiments seem to demonstrate that normal secretory endometrium can be brought about in the majority of the cases by the pregnant mare's serum alone.

Short summaries of four cases, which are particularly interesting in comparing two other potent products (anterior pituitary extract from sheep and a mixture containing anterior pituitary extract and chorionic gonadotropin [synapoidin]), are given. Detailed discussion of the latter products are too lengthy for this paper.

CASE 1.—Menses which began at 13 years of age were irregular until the patient reached the age of 15 when amenorrhea occurred for twenty months. Repeated biopsies showed atrophic endometrium. After

three months' treatment with gonadogen (60 units each month), the patient had one menstrual period. Gonadogen was repeated for nine months during which time the biopsies showed slight growth effect, then reverted to consistent atrophic endometrium. After twelve months of treatment, gonadogen was discontinued and anterior pituitary extract from sheep was given each month in dosages from 100 to 300 hypophyseotomized rat units. After two months, the endometrium showed slight hyperplasia with no secretion and regular menstrual periods began. The anterior pituitary extract was continued every month, and biopsies before each period showed interval nonsecretory endometrium or endometrial hyperplasia with "Swiss cheese" glands. After thirteen months of steady treatment with anterior pituitary extract, late interval secretory endometrium was first obtained. After the fifteenth month normal premenstrual endometrium was found. Treatment with anterior pituitary extract was continued monthly and 8 of the next 11 consecutive monthly biopsies showed secretory endometria. The last biopsy was nonsecretory and was the only cycle in which anterior pituitary extract had not been given in twenty-four months. In this case, the anterior pituitary extract has given normal secretory endometrium when the pregnant mare's serum was ineffective.

CASE 3.—Patient, 21 years old, had had regular menses from the age of 13 to 20, but had had none for seven months when first seen. Biopsies showed nonsecretory endometrium. Gonadogen was given each month for nine months. No menses occurred. Biopsies remained nonsecretory, at times atrophic. In the next twelve months, the patient received anterior pituitary extract from sheep. Two menses occurred. Biopsies remained nonsecretory but showed fair growth effect. In the next twelve months, the patient was given synapoidin each month. She had three menses. Biopsies taken each month showed consistently nonsecretory endometrium. The pregnant mare's serum was followed by no menses, anterior pituitary extract and synapoidin were each followed by occasional menses, but at no time did secretory endometrium occur.

CASE 6.—Patient, 23 years old, had had amenorrhea for fourteen months. Biopsies showed nonsecretory endometrium. Gonadogen was given each month for twenty months, resulting in cyclic menstruation. Secretory endometrium (twice full premenstrual) was found 3 times and nonsecretory 9 times. Menses stopped after two months. Four months later anterior pituitary extract from sheep was given for five months, during which time she had three menses with nonsecretory endometrium. Treatment was discontinued. In the next six months no menses occurred. The pregnant mare's serum hormone was followed by menses and occasional secretory endometrium. Anterior pituitary extract was followed by menses but no secretory effect.

CASE 12.—The patient began menstruating for the first time in thirteen months after one series of gonadogen. Injections were continued each month for twelve months. Biopsies taken each month before the menses showed secretory endometrium twice and nonsecretory nine times. Once there was slight endometrial hyperplasia. The injections were changed to synapoidin each month for seven months. Secretory endometrium occurred twice and nonsecretory five times. In this case, synapoidin (a mixture of chorionic gonadotropin and anterior pituitary extract) seemed to give the same secretory effects as the pregnant mare's serum hormone.

TABLE II. ENDOMETRIAL HYPERPLASIA WITH METRORRHAGIA

CASE	AGE	DURATION	P.M.S. UNITS	OBSERVED	RESULT	FOLLOW-UP BIOPSY
1	20	4 yr.	200	6 mo.	Regular menses 6 mo. Recurrence	Hyperplasia
2	25	8 yr.	260	16 mo.	Not improved	Hyperplasia
3	23	2 yr.	350	6 mo.	Not improved	Hyperplasia
4	18	5 yr.	140	2 mo.	Not improved	Hyperplasia
5	25	4 mo.	90	1 mo.		Hyperplasia
6	43	2 yr.	120	6 mo.	Not improved	Secretory
7	23	5 yr.	120	12 mo.	Improved 8 mo. Recurrence	Hyperplasia
8	28	10 yr.	180	30 mo.	Temp. improved	Hyperplasia

METRORRHAGIA

Eight patients with metrorrhagia and proved endometrial hyperplasia with "Swiss cheese" glands and nonsecretory epithelium have been treated with pregnant mare's serum hormone. The total dosage has varied from 90 to 350 units. Four patients were not improved in any degree. Three had fairly regular normal menses for six to twelve months, after which there was recurrence of the metrorrhagia. The recurrence was helped in 2 cases, while one recurred a third time when the bleeding did not stop after the hormone. Follow-up biopsies showed no change in the hyperplastic endometrium in 7 cases. One patient, aged 43 years, did show a premenstrual endometrium on two occasions after the hormone was given. This patient was found at operation to have a small submucous myoma. The results in these 8 cases were not very encouraging for the treatment of endometrial hyperplasia.

Ten other patients with metrorrhagia have had endometrial biopsies which failed to show hyperplasia. Three had secretory endometrium before, during, and after treatment, but the metrorrhagia continued without improvement. Seven patients showed interval nonsecretory endometrium before treatment. Three had regular menses; the patients were followed for from six to fourteen months. One of these remained anovulatory, the second showed early secretion in one cycle and no secretion in three cycles, while the third had normal premenstrual endometrium on two occasions. Three patients remained unimproved as far as regulating the bleeding was concerned, but during treatment 2 showed early secretory endometrium.

TABLE III. METRORRHAGIA WITH BIOPSY

CASE	AGE	BIOPSY	TREATMENT UNITS P.M.S.	OBSERVATION	RESULT	BIOPSY AFTER TREATMENT
1	20	Premenst.	250	3 mo.	Not imp.	Same
2	29	Premenst.	60	4 mo.	Not imp.	Same
3	29	Slight secretion	330	6 mo.	Not imp.	Slight secretion
4	18	Nonsecretory	60	6 mo.	Regular	Nonsecretory
5	16	Nonsecretory	200	6 mo.	Imp.	Slight secretion
6	22	Nonsecretory	30	14 mo.	Regular	Secretory
7	18	Nonsecretory	140	8 mo.	Not imp.	Slight secretion
8	15	Nonsecretory	60			
9	29	Nonsecretory	150	12 mo.	Not imp.	Slight secretion
10	22	Nonsecretory	60	9 mo.	Not imp.	

Only 3 out of 10 patients were clinically relieved of the metrorrhagia. Four of 7 patients with anovulatory endometrium showed some degree of secretion in the endometrium during treatment. This would suggest that some response was obtained in the ovary and that the treatment may have been incomplete. As yet the treatment of metrorrhagia has not been simplified.

Nine additional cases of metrorrhagia have been treated without biopsies. Five had puberty metrorrhagia; the ages of the patients varied from 9 to 15 years. At least very good temporary results have been obtained in 4 cases, although one patient has had a recurrence after eight months. One of these girls developed a temporary painful cystic ovary during treatment. The other four patients had only slight bleeding between periods. Three seemed to be improved and one showed no improvement.

A study of these 27 cases of metrorrhagia suggests that the pregnant mare's serum hormone is of value in about one-half of the cases. Possibly one-half of the cases might improve anyway. The finding of secretory effects in 5 anovulatory bleeding cases does suggest that ovarian stimulation has taken place. The series of puberty metrorrhagia is too small for conclusions, but does suggest the possible use of pregnant mare's serum hormone in these cases.

TABLE IV. METRORRHAGIA WITHOUT BIOPSY

CASE	AGE	DURATION	TREAT- MENT UNITS P.M.S.	OBSERVATION	RESULT
1	13	4 mo.	70		
2	9	7 mo.	60	9 mo.	Normal 8 mo. Recurrence
3	14	3 mo.	60	3 mo.	Normal. Cystic ovary
4	15	3 mo.	60	3 mo.	Normal
5	14	6 mo.	240	5 mo.	Normal
6	26	6 mo.	60	1 mo.	Improved
7	32	5 mo.	120	3 mo.	Not improved
8	25	1 mo.	30	6 mo.	Normal
9	29	2 mo.	60	6 mo.	Improved

DYSMENORRHEA

The treatment of dysmenorrhea is one of the most difficult problems in gynecology. Innumerable remedies have been offered. The whole matter is so confusing and unsatisfactory that one feels there is no dependable therapy.

Dysmenorrhea may be readily classified into two types, the secondary or extrinsic type and the primary or intrinsic type. The secondary group includes those due to definite cervical strictures, intramural or submucous myomas of the uterus, chronic salpingitis with menstrual exacerbations, and various pelvic tumors. An exceedingly important and common cause is endometriosis, with either adenomyomas of the uterus or implants in the abdominal cavity. Endometriosis may be suspected when an ovary is adherent and more readily diagnosed when there are palpable densely adherent cysts or nodules and induration in the rectovaginal septum. On the other hand, the preoperative diagnosis may be impossible because of the small size of the implants. Some

TABLE V. DYSMENORRHEA

CASE	AGE	RACE	BIOPSY BEFORE TREATMENT	TREATMENT UNITS PER MONTH	BIOPSY AFTER TREATMENT	OBSER- VATION	IMPROVE- MENT	REMARKS
1	20	C	Premenst.	60-30-60-60- 50-60	Premenst. 1 x	16 mo.	Moderate	Pregnant 10 mo. later
2	15	C	Premenst.	30-60-60-60	Premenst. 4 x	21 mo.	Marked	
3	19	C	Premenst.	60-60-60-60- 60-60-60	Premenst. 4 x	23 mo.	Slight	Operation old ruptured ap- pendix
4	22	C	Premenst.	50-60-60-60- 60-50	Premenst. 2 x	23 mo.	Marked	
5	14	C	Early secret.	60-10		2 mo.	None	Later active tuberculous lungs and salpingitis
6	17	C	Premenst. 3 x	60		4 mo.	Slight	Pregnant after 4 mo.
7	17	W		60-60	Nonsecret. 3 x	15 mo.	Marked	
8	21	W	Premenst.	60-30-30-30- 60-60-60	Premenst. 6 x	8 mo.	None	Operation: endometri- osis
9	16	W		60-100-40- 50		9 mo.	Moderate	
10	21	W		60-60-60-60		12 mo.	Moderate	Temporary cyst after fourth series
11	24	W		60-60-60		16 mo.	None	Marked ante- flexion
12	21	W		60-60-60		9 mo.	Slight	Pregnant 6 mo. later
13	21	W		60-60-60-60		10 mo.	None	Adherent ovary: ?en- dometriosis
14	23	W		70-60		3 mo.	Worse	Operation: endometri- osis
15	28	W		60-60-60-60 60-60-60-60 60-60		18 mo.	Marked	
16	30	W		60-60		8 mo.	Moderate	
17	20	W		750-1000- 1000 (An- teron)-60- 60		11 mo.	None	Marked ante- flexion
18	23	W		60-60-60-60		18 mo.	Marked	
19	30	W		60-60-60-60 60-60-30		12 mo.	Marked	Cystic ovary 2 x
20	17	W		60-60		7 mo.	Marked	Pregnant
21	30	W		750 (An- teron)		9 mo.	None	Cure after stem pessary
22	27	W		60		7 mo.	None	Local reac- tions. Ad- herent ovary: ?en- dometriosis
23	21	W		60-60-60- 60-60		8 mo.	Marked	
24	19	W		60-60-60-60		4 mo.	Marked	
25	24	W		60-60-60		10 mo.	Moderate	
26	21	W		60		8 mo.	Slight	
27	22	W		60-60		3 mo.	Moderate	
28	24	W		60-60-60		8 mo.	Moderate	
29	21	W		60-60-60-60		10 mo.	None	Anteflexion. Stem pessary with relief
30	13	W		30-30		2 mo.	Marked	

intractable cases with supposedly primary dysmenorrhea are actually due to endometriosis. Recurrent menstrual appendicitis may be a factor in some cases. The pain may be caused by ureteral obstruction in the form of spasm or stricture.

Primary dysmenorrhea is applied to those cases in which no pathology can be demonstrated, other than variations in size and angulation. There is difference of opinion as to whether angulation and the small canal constitute sufficient etiology to place these cases in the secondary group. Most authors consider them primary, feeling that the etiology is of developmental or endocrine origin.

In the majority of patients with primary dysmenorrhea, the history includes the usual menarche at about fourteen years with painless supposedly anovulatory menses for some two years. During this time, the uterus is of the small juvenile type. At sixteen years of age, cramps appear, apparently associated with beginning ovulation. From eighteen to twenty years of age the pain is often very severe and the uterus is usually adolescent in type, being perhaps of normal length but quite narrow. Between the ages of 22 and 25, the pain diminishes to a mild, undisturbing cramping, and the body of the uterus particularly is found quite well developed. There are, of course, exceptions to this sequence, but it is the commonest that we have seen.

Psychiatric factors, thyroid, iodine, malnutrition, lack of exercise, and systemic disease have been brought out as important in treatment.

Endocrine influences are incompletely understood. The estrogenic hormones directly regulate the size of the uterus in proportion to the amount of hormone present, unless the uterus as a receptor has some degree of insensitivity. Treatment has been directed to developing the uterus by additional estrogens parenterally. Sturgis and Albright⁷ have found that the subsequent period will be painless if large doses of estrogens, which prevent ovulation, are given early in the cycle. Although not too encouraging, it does seem that estrogens over a long period of time may have a lasting effect in relieving dysmenorrhea in some cases.

Progesterone is of value in certain cases when the uterus is well developed, and prolonged relief may follow therapy given over a few months. Testosterone seems effective by depressing the pituitary and ovary and preventing ovulation, but probably gives no lasting cure. Chorionic gonadotropin is of questionable value in the treatment of any woman.

In a previous paper (Gray and Manly, 1940) the pregnant mare's serum hormone seemed of value in the treatment of patients with dysmenorrhea. A longer follow-up of the earlier cases and other new cases are here reported.

Thirty women have been treated with the pregnant mare's serum hormone for supposedly primary dysmenorrhea. Only patients with marked pain are included. The age varied from 13 to 30, averaging twenty-one years. Twenty-four were white and 6 were colored.

One or more endometrial biopsies were taken immediately before menstruation and preceding treatment in 7 cases. Six showed premenstrual secretory endometrium and one showed questionable early secretion. The following month the latter case was found to have active pulmonary tuberculosis and apparently acute salpingitis. Biopsies were taken during and after treatment in 7 cases, showing normal premen-

strual endometrium in six. One patient (Case 7) had 3 biopsies taken after treatment which showed nonsecretory endometrium. These 3 menses were entirely painless, but several other periods were associated with slight cramps and may have been ovulatory cycles. The evidence in the other 6 cases indicates that the ovaries were ovulating when severe pain was present and that treatment did not interfere with ovulation.

Nine patients in this series had practically complete relief of menstrual pain. Eight had moderate relief, being much improved. Four had only slight relief. Two of the latter were treated only one month, and a third one at exploratory operation had an old ruptured appendix.

Nine patients in this series had no relief from treatment. Two (Cases 21 and 29) had stem pessaries with subsequent relief, and two (Cases 11 and 17) had very small uteri with marked acute anteversion. The latter we believe should have stem pessaries. Two (Cases 8 and 14) had exploratory operations with findings of numerous minute endometrial implants. In each of two patients (Cases 13 and 22), there was a slightly adherent ovary, and the patients have been advised to have exploration for possible endometriosis. Tuberculosis was discovered in the ninth patient (Case 5) after one month's treatment, and treatment was discontinued.

The general impression of efficacious therapy has been obtained in this study. It has seemed that the uteri in most cases have developed rapidly from the adolescent to more adult size. In some there has been varying regression in size after discontinuing therapy, with largely maintenance of improvement. Evidently certain of the failures were actually secondary dysmenorrheas. During treatment, two patients developed painful cysts which regressed in the subsequent cycle. Four patients became pregnant shortly after treatment, one (Case 19) having complained of sterility for six years.

MALE STERILITY

Previous to the past eighteen months our work in sterility included only the most cursory studies of the male. Huehner tests and direct microscopic examinations of condom specimens often give entirely false impressions. The former may show the effect of female secretions, but nothing regarding the number of spermatozoa. Either the rubber or powder in condoms so alters the viability and count as to make observations undependable, as reported in recent literature. Therefore, we made sperm analyses from masturbated specimens, including gross appearance, volume, liquefaction time, pH, motility, total count, and differential count of stained smears. While these many points are important in evaluating the fertility of a man, it seems that the total count per cubic centimeter is the most important determination, as the other characteristics generally follow variations in the count. As stated in the literature by Hotchkiss⁸ (1936) and others, 60 millions per c.c. seems to be the lower limit of normal, relative sterility being below this number, approaching absolute sterility of zero.

In the past, hormone therapy for sterility in men has been very discouraging. Looney⁹ (1940) reported a single case thoroughly studied and treated with pregnant mare's serum hormone. In that case the sperm count rose from 32 millions to 133 millions. Conception could not occur because the wife had nonpatent tubes. Heckel¹⁰ (1940) re-

TABLE VI. STERILITY IN MEN

CASE	AGE	MILLIONS PER C.C. BEFORE TREATMENT	TREATMENT UNITS P.M.S.	MILLIONS DURING TREATMENT	FINAL COUNT
1	45	1.2	550	6.5	3.1
2	39	35.0	140		
3	33	22.5	290	35.0	180.0
4	30	0.6	400	117.0	
5	36	32.0	200	15.0	51.8
6	32	30.8	300	57.5	Normal pregnancy. Count 15 mo. later 374
7	32	22.5	360		415.8
				19.6	
				35.6	Pregnancy, miscarriage
				67.9	
8	48	5.0	120		5.0
9	30	Small number	750 A.P.E.*		Normal pregnancy
		2.5	120 P.M.S.*	12.5	
			740 A.P.E.	1.6	
			200 P.M.S.	2.5	
				0.4	0.4
10	34	29.5	200		
11	28	42.8	Thyroid	64.9	76.6
12	30	6.2	Thyroid	36.2	
				67.2	4.5
13	27	None	Thyroid	One sperm	
14	52	1.8	None		
15	49	2.5	None		
16	34	7.5	None. Active tuberculosis		
17	37	None	None		
18	30	None	None		

*A.P.E., anterior pituitary extract; P.M.S., pregnant mare's serum.

ported a single case with increase in count from about 50 millions to 219 millions with this hormone. After nine months without treatment the count was 56 millions. Charny¹¹ (1940) reported 5 patients treated with the pregnant mare's serum hormone. Three showed definite improvement in the count although in none had the count increased to normal.

The husbands of 45 private patients complaining of sterility have had sperm analyses from masturbated specimens. Eighteen (40 per cent) of these men had sperm counts below 60 millions per c.c., considered an important factor in the sterility of these couples. Fifteen (33 per cent) were considered relatively sterile and three (7 per cent) absolutely sterile.

Of the 15 relatively sterile men, two were not encouraged to take treatment because of their age (49 and 52 years). One was not treated specifically, because his routine physical examination revealed unsuspected active pulmonary tuberculosis. Of the remaining, two with hypothyroidism showed increase to normal counts with thyroid alone, although one was a little irregular in taking the thyroid, and the count fell to 4.5 millions in six months.

Ten men have been treated with the pregnant mare's serum hormone for relative sterility. Four had previously taken thyroid, apparently without effect. Very definite increases in the count occurred in five after the use of gonadogen. In one (Case 5), there followed a full-term normal pregnancy (two miscarriages had occurred five and six years earlier). In another instance (Case 7), there was a pregnancy ending

in miscarriage. Two patients (aged 45 and 48) showed no improvement whatever. A third patient without improvement (Case 9) was most interesting. Three years ago this man, aged 27 years, had a very small number of sluggishly motile sperm. (At that time sperm counts were not being made by us.) Fifteen injections of sheep's anterior pituitary extract were given; there followed a full-term normal pregnancy. Six months ago he returned because of sterility. The count showed 2.5 millions. All treatment has been unavailing in further sperm stimulation, including a series of pregnant mare's serum hormone, a series of sheep's anterior pituitary extract, and a second series of pregnant mare's serum hormone. The basal metabolism was normal. At present, for the first time, he is receiving thyroid to tolerance. After one month there has been no improvement. In the two remaining cases counts have not been obtained after treatment.

In this series the dosage was usually 10 units three times weekly, although some received 20 units three times weekly. Total dosages of 200 to 550 units were employed. It is possible that in some cases far larger amounts should have been given. One patient (Case 8) had local reactions, but continued for twelve injections.

Our records apparently have indicated stimulating effects in five men from the pregnant mare's serum hormone and failures in three cases. Two failures were in individuals 45 and 48 years old, the oldest in the series, and one of these had recurrent chronic osteomyelitis. One other failure was in a young man who seemingly responded three years earlier to anterior pituitary extract.

SUMMARY

1. The effect of the pregnant mare's serum hormone in the form of "gonadogen" has been studied in 83 cases in the past three years.

2. In 16 patients with secondary amenorrhea, treated from one to nineteen months, 12 menstruated and 2 were refractory after nine and twelve months of continuous treatment. In the 12 who had cyclic menstruation under treatment, 6 showed a secretory and 4 a nonsecretory endometrium. In these 6 cases, 12 cycles were secretory and 24 anovulatory. One case was followed immediately after one secretory biopsy by normal pregnancy.

3. In 8 patients with endometrial hyperplasia, 4 showed some clinical improvement, although 3 relapsed. The endometrial hyperplasia remained the same in 7, while one developed premenstrual endometrium.

4. In nineteen other patients with metrorrhagia, 10 showed clinical improvement, although somewhat equivocal. Four of 7 patients with anovulatory endometrium had varying degree of secretion in the endometrium during treatment. This suggests some active effect from the hormone.

5. In 30 patients with supposedly primary dysmenorrhea, 21 were improved (9 marked, 8 moderate, 4 slight). Of the 9 failures, secondary factors entered practically every case. Four patients became pregnant during or shortly after treatment.

6. Temporary painful cysts of the ovary occurred in 5 women: they disappeared with the following cycle. Further treatment was accompanied by recurrence of the cyst in one case.

7. In 10 men with relative sterility, 5 were improved and 3 remained unimproved. One full-term normal pregnancy and one miscarriage were obtained in these couples.

8. No serious sensitivity reactions occurred in any case.

The equine gonadotropin used in these cases was entirely in the form of gonadogen, very generously supplied by the Upjohn Company, except in two cases where anteron was used, supplied by the Schering Corporation. The anterior pituitary extract mentioned in follow-up studies of certain patients with amenorrhea was furnished by the Winthrop Chemical Company. Synapoidin was supplied by Park, Davis and Company.

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DISCUSSION

DR. EUGENE H. COUNTISS, NEW ORLEANS, LA.—It would be interesting if Dr. Gray would tell us something of the change in the ovaries in these cases with manipulation and curettage. Were small follicular cysts ruptured, thus allowing a more normal corpus luteum factor?

We now know that a disturbance of gonadotropic function is not the same in primary as in secondary amenorrhea, and that excessive production of gonadotropic hormone could be the cause of secondary amenorrhea.

Dr. Gray would lead us to believe that in cases of menorrhagia, pregnant mare's serum is not of much value. Hyperhormonal bleeding is due to disturbed gonadotropic secretion in the anterior pituitary, and male sex hormone acts by directly inhibiting gonadotropic secretion of the anterior pituitary. In the cases of endometrial hyperplasia, 50 per cent gave failures, while 4 were enough improved to encourage treatment with pregnant mare's serum. They all became refractory later and returned to the nonsecretory state.

In the 30 patients with dysmenorrhea treated with pregnant mare's serum, relief was obtained often enough to warrant further trial.

In managing male sterility, I would like to stress the importance of the masturbated specimens, as these alone offer a true evaluation.

DR. L. W. MASON, DENVER, COLO.—One has to be extremely careful in clinical evaluation when giving hormone preparations to a woman whose machinery, may I say, is intact. Whenever I feel my feet getting off the ground in enthusiasm at results which I seem to be obtaining by treatment, I think of the 16 cases of amenorrhea that Dr. R. G. Gustavson of the Department of Chemistry at the University of Colorado and I were studying several years ago from the standpoint of estrin

determinations. Before we could complete the study, 5 of the individuals had menstruated spontaneously.

One would think that the ideal indication for the pregnant mare's serum would be those cases in which the only abnormality found was a deficient menstrual endometrium. I have two slides each from three sterility cases which were thoroughly studied, and which fall into that group.

1. The first slide is one of several biopsies taken at the beginning of menstruation, none of which showed any evidence of ovulation. The patient was given three intramuscular injections of gonadin in 200 unit doses three times a week, and 600 units just before the time of expected ovulation. This was repeated over several months, with increasing dosages. The next slide of this case, taken three months after beginning treatment, shows, I think, some improvement in the endometrium, which, however, is still markedly deficient in secretory activity. Whether this improvement is spontaneous or resulted from the treatment, I do not know.

2. The slide from the second case, before treatment, shows evidence of ovulation, because there are secretory changes in the glands, but you will all agree that it is far from normal. This patient was given various combinations of dosages at various times during the next several months. The second slide of this case, taken several months after beginning treatment, shows an endometrial picture which is inferior to the first one, before treatment was instituted. Was this spontaneous, or the result of treatment?

3. The first slide from the third case shows definite evidence of ovulation, but it shows, I consider, a deficiency in secretory activity. This patient was given large doses of pregnant mare's serum (2,000 units) at various times through a period of several months. The second slide, after two months' treatment, shows what appears to be a characteristic cystic glandular hyperplasia. This was in a woman in her early twenties, whose menstrual history had always been essentially normal. This change may be spontaneous, but it may also be due to the very large doses of the serum. It may be that in such dosages, the material may stimulate multiple follicle formation, without normal evolution and corpus luteum formation, so that we get the picture we see in the typical menopausal cystic hyperplasia.

In none of these cases did pregnancy occur, and Mazer and Israel, in their new book, find its use disappointing in the treatment of sterility. I think this last slide will show the wisdom of keeping before our minds the motto which appears in the delivery rooms at the Chicago Lying-in Hospital: *Primum Non Nocere*—first do no harm. These newer hormone preparations are potent, and if they do not always do what we want them to do, they doubtless do something.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—Our results with pregnant mare's serum at the Jefferson Davis Hospital have been such that we do not advocate its use in women. For a study of the effects of this substance we selected a group of approximately 10 women who gave a history of normal menstruation. An endometrial biopsy was taken on these women on the first day of their menstruation and all the endometriums were premenstrual. Some individuals were given 1,000 international units, some 3,000 international units, some 6,000 international units, some 12,000 international units of pregnant mare's serum, every day or every other day or once a week, for approximately nine months. Endometrial biopsies were taken every month and in some cases every other month. In not one case did the menstrual cycle change from that previously recorded, which was normal at the beginning of treatment. All of the endometrial biopsies taken on the first day of menstruation still showed premenstrual endometrium. Pregnant mare's serum should have stimulated these normal ovaries so much that an irregularity of the menses should be produced. In view of this failure what can we expect pregnant mare's serum to do to abnormal ovaries?

If we gave synapoidin, a combination of A. P. L. and pituitary synergist, we obtained a definite upset in the menstrual rhythm. Synapoidin apparently will replace pregnant mare's serum.

DR. GRAY (closing).—Much of the accurate work with negative results has followed the use of a commercial preparation marketed in solution. Such solutions may be unstable. Results should be interpreted in the light of whether the dried product or prepared solution is used.

GYNECOGRAPHIC AID IN THE DIAGNOSIS OF ECTOPIC PREGNANCY*

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IT IS well recognized by the medical profession that ectopic pregnancy presents a confusing and decidedly inconsistent clinical picture. This is entirely comprehensible if we consider four conditioning factors, namely: (1) the variety of extrauterine locations; (2) preexisting pathologic conditions of these sites; (3) the duration of extrauterine pregnancy in a given site; and (4) occasional re-implantation of the ovum in another situation. The various types of implantation in the Fallopian tube, intramural, isthmie, ampullar and fimbrial, may give rise to differing syndromes, and the ovarian, abdominal, and cervical pregnancies create dissimilar symptoms. Previous inflammatory tubal disease and functional ovarian swellings often present elements which add to the confusion. Both the location and the duration of ectopic implantation are significant in relation to the severity of attack, the amount of hemorrhage, and to some extent, the prognosis.

The symptoms at onset are commonly those which are typical for normal intrauterine pregnancy, but in some cases, these are entirely lacking and the first intimation of the existence of pregnancy may be the sudden occurrence of severe pain, shock, and signs of intraperitoneal hemorrhage.

The diagnosis of ectopic pregnancy depends chiefly upon a carefully considered history and the findings on bimanual examination, but that there is no *reliable* typical history is well recognized; in some cases, even the most usual symptoms may be lacking. Upon examination, furthermore, in early cases there is often *no palpable swelling* or mass to be found, so that the diagnosis rests chiefly upon exceptional tenderness of the affected side.

Because of the protean nature of this disorder and the frequency with which it fails to follow a typical pattern, many diagnostic aids to facili-

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tate recognition of ectopic pregnancy have been described. It is especially in those cases in which the diagnosis is obscure, the differential difficult, and a decision urgent, that diagnostic aids other than those ordinarily employed are indicated. The prime object in utilizing additional aids is to decide upon prompt surgical intervention when the diagnosis of ectopic pregnancy is thereby established, and also to avoid laparotomy in cases simulating the picture of ectopic pregnancy but in which operation should not be performed. Many careful surgeons and gynecologists have operated for tubal pregnancy only to be embarrassed to find that both Fallopian tubes were normal and the pregnancy was intrauterine. Subsequent inquiry sometimes reveals that the patient herself produced the misleading symptoms by the ingestion of oxytocic drugs intended as abortifacients; furthermore, that the facts were purposely withheld from the physician in the hope of getting rid of an undesired pregnancy. Willful deception as well as inaccurate recital of symptoms must be taken into consideration in obtaining a history.

Whenever the usual symptoms of early pregnancy, such as delayed menses, breast fullness, nausea, and urinary frequency, are followed by irregular but slight bleeding and some colicky pains, the presence of tubal pregnancy should be considered likely. When, in addition, acute adnexal tenderness is found, the diagnosis is more certain. If a definite, soft, and very tender mass is palpable, the diagnosis is practically assured. However, inasmuch as many other pelvic conditions may produce symptoms and signs quite similar to those of ectopic pregnancy, a careful differential diagnosis must be made. Conditions mainly to be ruled out are: intrauterine pregnancy with or without threatened abortion; chronic salpingitis, hematosalpinx; cysts of the ovary, especially the corpus luteum cyst; torsion of the ovary or adnexa; acute appendicitis; retroflexed gravid uterus; intraperitoneal bleeding from a ruptured follicle or corpus luteum cyst.

The unruptured, early ectopic pregnancy presents the chief diagnostic problem, for after tubal rupture the picture changes so characteristically that the diagnosis is usually simplified. In this communication relating to the use of gynecography, only the diagnosis of unruptured ectopic pregnancy and tubal mole will be considered. Radiographic methods of diagnosis have been described by others, chiefly for cases of advanced ectopic pregnancy, especially abdominal pregnancy. In such cases, the fetal skeleton has been demonstrated outside the uterus, and the uterine cavity visualized by a sound or by means of the instillation of opaque media.¹ The identification of a small, empty uterine cavity by such means serves as conclusive evidence in abdominal pregnancy.² Snow³ has shown in addition that by soft tissue x-rays, the placenta, uterine wall, and amniotic sac can be demonstrated. The lack of uterine wall shadow over the fetus, he believes, is an important clew in the diagnosis of abdominal pregnancy.

In order to establish a diagnosis of ectopic pregnancy, the diagnosis of an existing pregnancy must first be made, and then a decision as to whether the pregnancy is intra- or extrauterine. In any case presenting the usual symptoms of early pregnancy in which spotting or early bleeding occurs, and especially if there is also some pelvic pain, extrauterine pregnancy must be considered likely. Irregular bleeding, usually slight, occurs in about three-fourths of the cases, and pain is characteristic of from 80 to 96 per cent of cases. It is rare to be able to palpate the very early unruptured tubal pregnancy; however, the discovery of a highly sensitive tube has great significance in suspicious cases.

Some of the signs and tests which may be of value for differential diagnosis become useful only after a certain amount of intraperitoneal bleeding has occurred, such as Cullen's "black umbilicus" (rarely observed), and blood obtained by cul-de-sac puncture. The Friedman test is usually positive in about half of the cases of ectopic pregnancies: Those in which the fetus is alive and/or chorionic tissue is proliferating. The drawback to its use is the forty-eight-hour delay. Perhaps the Falls' colostrum skin test will prove reliable as a substitute after more extensive trial. The advantage of the Falls' test is that the reaction appears within one hour. Both of these tests, however, may prove positive in the presence of a corpus luteum cyst, one of the chief conditions to be differentiated, and therefore cannot be considered conclusive. A positive pregnancy test usually implies a living ovum or at least, growing chorionic tissue; then the question of the intra- or extrauterine site must be decided. Blood counts are of little value early, for it is only when intraperitoneal bleeding occurs that the white blood count is increased, and the sedimentation rate remains normal until considerable hemorrhage and anemia occurs. These tests do not indicate the state of the ovum in the tube or the presence or absence of decidua.

The value of diagnostic curettage has been a matter of considerable controversy. When a definite decidua and complete absence of chorionic villi is found upon curettage, the diagnosis of extrauterine pregnancy is supported, but according to Novak,⁴ in only about one-half the cases is decidua found.

Heaney⁵ makes the point that a "dry scrape," in which no tissue is obtained, in a suspect case is almost certain evidence of ectopic pregnancy. He states that the fewer the scrapings, the more probable the presence of ectopic gestation, as most patients expel the decidual cast before coming to operation. Siddall and Jarvis⁶ state that while the findings of decidua without villi is strong presumptive evidence of extrauterine pregnancy, the absence of decidua is not reliable evidence against its presence. Rock,⁷ on the other hand, is of the opinion that curettage for the recovery of decidua without villi is rarely if ever desirable. It is in the cases in which the Aschheim-Zondek or Friedman tests are negative that there is usually no decidua in the uterus. Goldblatt and Schwartz⁸ found that there was a close but not perfect relationship be-

tween the state of preservation of the chorionic tissue and the Friedman test, and the latter was not always directly related to the presence of decidua. The presence of decidual reaction in the uterus depends, they believe, upon the duration and amount of uterine bleeding. They agreed with Siddall and Jarvis that patients with ectopic pregnancy who bleed scantily may show uterine decidua but with decreased expectancy as the duration of bleeding increases; those patients who bleed moderately or profusely for more than three weeks are extremely unlikely to have a uterine decidua.

Biopsy specimens of decidua may be obtained in suspected cases by means of the suction curette, but if intrauterine pregnancy has not been definitely ruled out, this should not be attempted. This advice appears sound in spite of Sturgis' report⁹ of 7 endometrial biopsies in intrauterine pregnancy without harmful results. It must be borne in mind, moreover, that decidua-like changes may occur in the absence of pregnancy due to progesterone effects¹⁰ and that there is no characteristic endometrial picture in ectopic pregnancy.

Cul-de-sac puncture has been accepted as a means of determining the presence of blood in the peritoneal cavity. It has no value, however, in cases of unruptured ectopic with the exception of cases of partial tubal abortion. Posterior colpotomy, however, is advocated as a diagnostic procedure by a number of authorities. Torpin¹¹ believes it should be done in every case where the diagnosis is uncertain, and Heaney⁵ prefers it to simple puncture, believing that the danger from the procedure is slight. Furthermore, if the pregnant tube is accessible, it may be removed through the colpotomy opening.

Peritoneoscopy has also been used successfully by Ruddock,¹² Hope,¹³ and others, but the method has not received general acceptance.

For the diagnosis of early and especially unruptured ectopic pregnancy, and for tubal mole, two methods of x-ray are available which may be grouped under the term "gynecography." One of these, hysterosalpingography, is dependent upon the use of an opaque substance, while the other employs a gaseous medium to produce pneumoperitoneum; i.e., pneumorocentgenography. The two methods may be used independently or combined with each other. By means of a contrast medium, the uterine cavity may be demonstrated on the x-ray film, as well as tubal lumen, when the tubes are open. In intrauterine pregnancy, the uterus is distensible and usually shows the imprint of the ovum in an enlarged cavity. In extrauterine pregnancy, the uterine cavity will usually be shown as normal in size, triangular or oval, but without the imprint. The tubes may or may not be patent, for if decidua fills the uterine ostia of the tubes, no contrast medium will pass. On the other hand, if the uterine decidua has been shed, both tubes may admit the medium, provided that they are not otherwise blocked by the pregnancy or by previous inflammatory damage.

Bortini¹⁴ reports that the diagnosis of early extrauterine pregnancy can be made by hysterosalpingography, the uterine shadow appearing triangular or slightly round, and the uterus slightly deviated to the affected side. If the ampulla is the site of tubal pregnancy, the opaque medium shows a characteristic distribution through this segment. Mathieu¹⁵ claimed that by hysterosalpingography a diagnosis of early tubal pregnancy could always be made (100 per cent!), and that in tubal abortion the mass can be visualized, the oil surrounding the mass rendering it radiopaque. Furthermore, he stated that when pregnancy was in the midportion of the tube, a rounded shadow appeared at the stopping point of the opaque medium; this he considered to be pathognomonic of tubal pregnancy. I have failed to observe this sign in my cases.

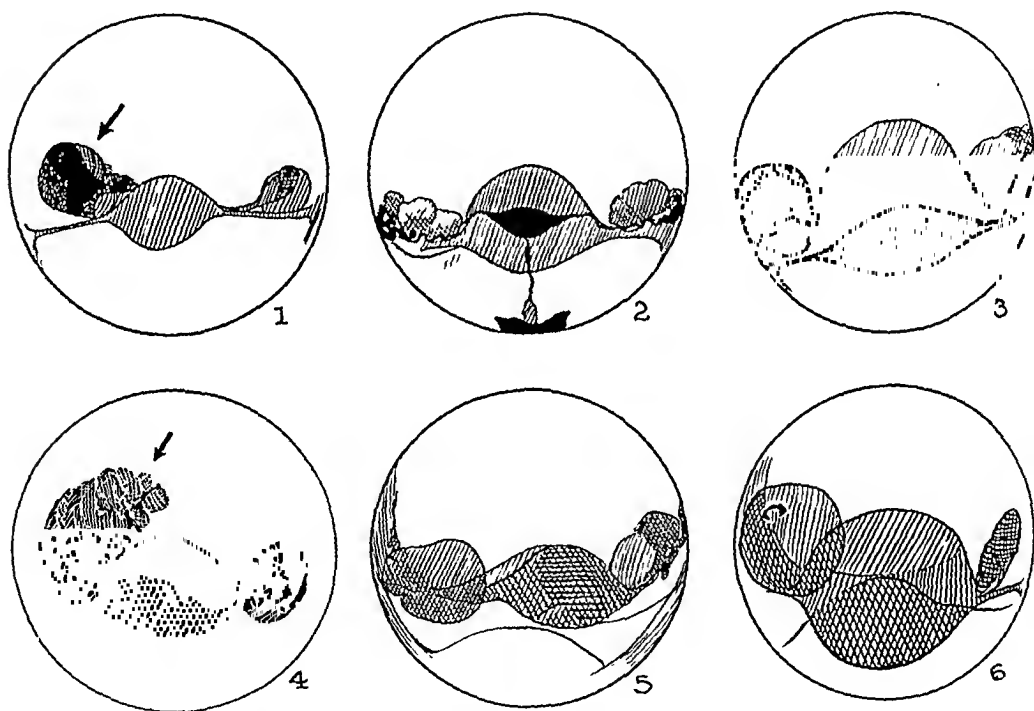


Fig. 1.—Differential diagnosis of ectopic pregnancy with gynecography. 1, Unruptured tubal pregnancy (transabdominal pneumoperitoneum); 2, normal uterus, ovaries and tubes (combined gynecography); 3, intrauterine pregnancy, 6 weeks (transabdominal pneumoperitoneum). Cases 4, 5, 6: Similar symptoms: Delayed menses, colicky pain, spotting. Similar findings: Tender mass on right side. 4, Unruptured right tubal pregnancy, blood in fimbriated end; 5, right lutein cyst; 6, pregnancy, 6 weeks; complicated by right twisted dermoid. (Note area of calcification.)

Pneumoroentgenography is no new procedure in gynecology. I¹⁶ have reported periodically the results obtained at Michael Reese Hospital and described the technique fully. I have employed the method in selected cases for almost two decades, particularly in cases of sterility and for gynecologic differential diagnosis. I first reported a case of tubal pregnancy diagnosed by pneumoroentgenography in 1926.* Its use in

*Surg., Gynec. & Obst. 42: 83, 1926.

ectopic pregnancy has been limited to cases of unruptured tubal pregnancy and the pelvic lesions which compete with it in diagnosis, and also cases of missed ectopic pregnancy which result in tubal mole. The method is not recommended for the acutely ill patient with shock or intraperitoneal hemorrhage.

Not infrequently, patients who have been under observation and treatment for sterility present symptoms suggestive of ectopic pregnancy. The bimanual findings often prove vague in such cases, and the Friedman test may be negative. Diagnostic curettage or even an endometrial

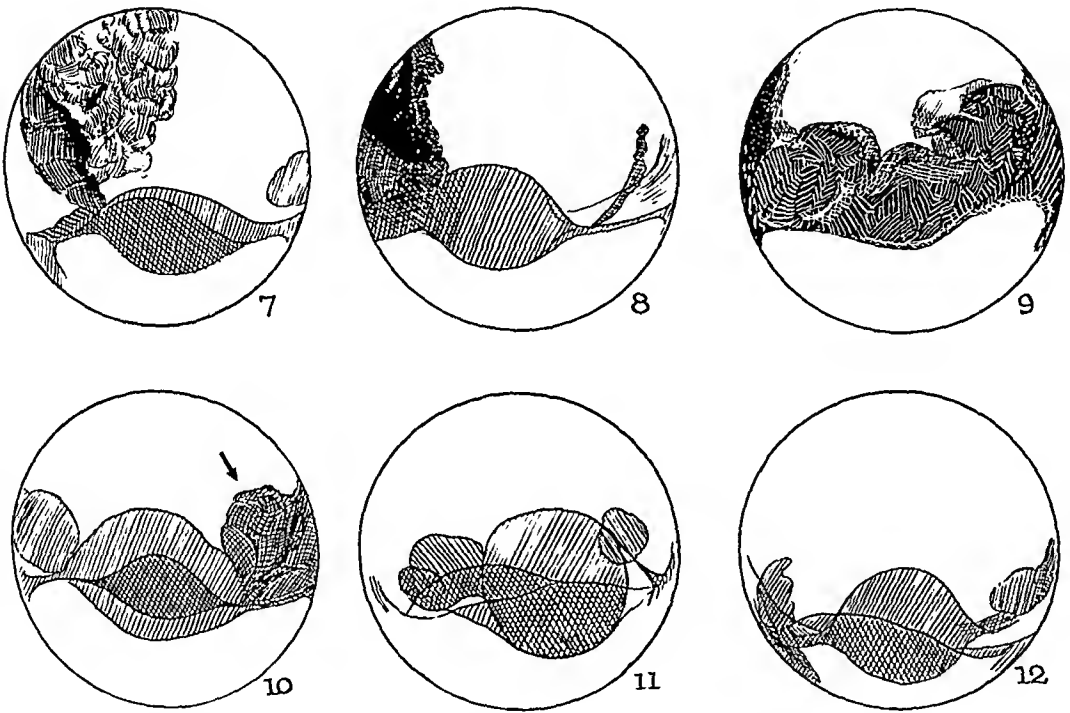


Fig. 2.—7, Right unruptured tubal pregnancy: Bleeding from fimbriated end; 8, unilateral inflammatory disease right adnexa: simulating picture of ectopic pregnancy; 9, bilateral inflammatory: Symptoms suggestive of ectopic pregnancy. Cases 10, 11, 12: Similar symptoms: Irregular or delayed menses, pelvic pain, tenderness. 10, Left tubal pregnancy: unruptured; 11, intrauterine pregnancy, 6 weeks: right ovary globular, tender; 12, normal pelvic viscera; sterility.

biopsy under such circumstances would be inadvisable unless intrauterine pregnancy were ruled out with certainty. Furthermore, even hysterosalpingography is not to be recommended, for, as I have consistently warned, all intrauterine instrumentation is contraindicated in a patient with suspected pregnancy, intra- or extrauterine. On the other hand, *transabdominal pneumoroentgenography* may be used without danger of disturbing a pregnancy. There are no contraindications to the use of this method in unruptured ectopic or intrauterine pregnancy. When a satisfactory film is obtained after pneumoperitoneum is induced, the patient being radiographed in the characteristic partial

knee-chest posture, a replica of the pelvic status appears in the film (Fig. 1). The uterus, tubes, and ovaries can be differentiated sufficiently to recognize tubal involvement. Ovarian cysts are easily ruled out as they appear as smooth, round structures separate from the tubes. Tubal pregnancy often appears as a dense, cone-shaped shadow, the apex arising from the uterine horn. The size depends upon the duration of the pregnancy. The ovary on the same side may be seen as a separate oval structure or may form part of the adnexal mass. In contrast, the

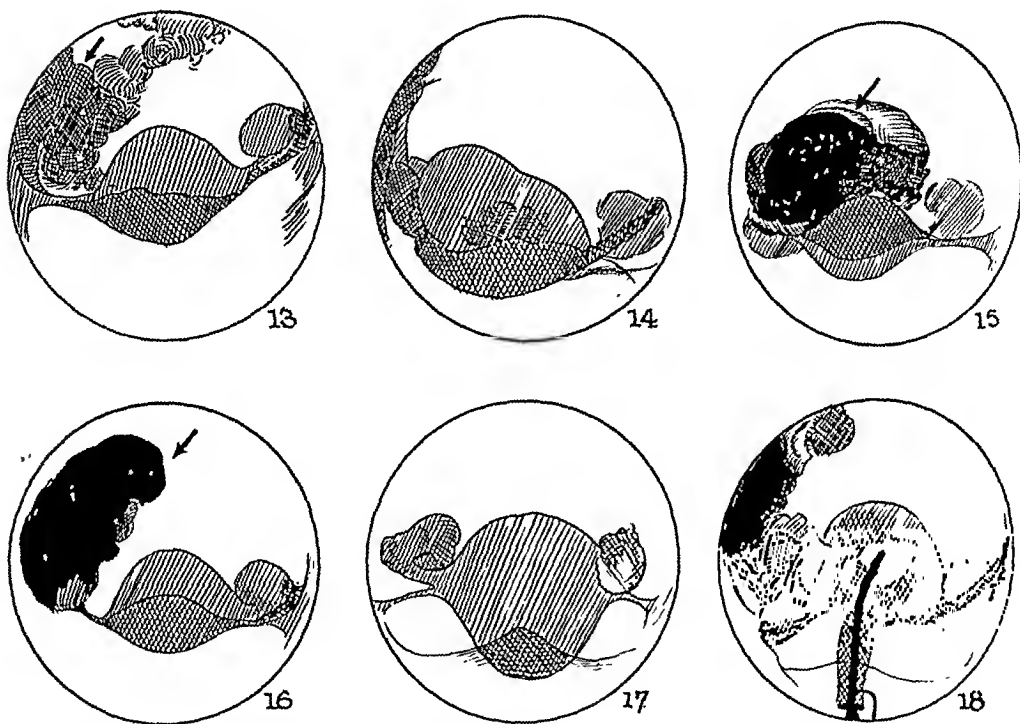


Fig. 3.—13, Right unruptured tubal pregnancy: slight bleeding fimbriated end; 14, intrauterine pregnancy, 7 weeks: symptoms simulating ectopic produced by oxytocic drugs; 15, right tubal pregnancy: partial tubal abortion; 16, right tubal pregnancy: unruptured; 17, intrauterine pregnancy, 6 weeks, acute anteversion; 18, right tubal obstruction: inflammatory disease (postabortal).

opposite adnexa appear normal, the tube and ovary being visualized. The uterus in some cases appears larger, and in some, normal in size. In cases where there has been pre-existing inflammatory disease, there will be increased density of both tubal shadows, and then the change in size and shape will be significant in diagnosis. When previous bilateral tubal damage has occurred and extensive pelvic adhesions are present, the picture is likely to be confusing. A small amount of blood in the peritoneal cavity does not interfere with the diagnosis in early unruptured and suspected tubal pregnancy. While the transuterine route is not used in suspected cases, in cases of old quiescent tubal pathology where the diagnosis of an ectopic must be considered, I have

combined the instillation of opaque media into the uterine cavity with the pneumoperitoneum to obtain complete gynecography of the pelvis (Fig. 5). In a few such cases, the combined method has proved of value in arriving at a correct diagnosis. Here we may observe that the contrast medium either stops abruptly at the point of tubal obstruction (by the implanted ovum) or *it breaks up into numerous small channels where it permeates the blood clot*. I have never observed that it surrounds the ovum in the tube in the characteristic way described by Mathieu. The greater information from this procedure accrues from the use of pneumoperitoneum, for the latter permits outlining the tubal

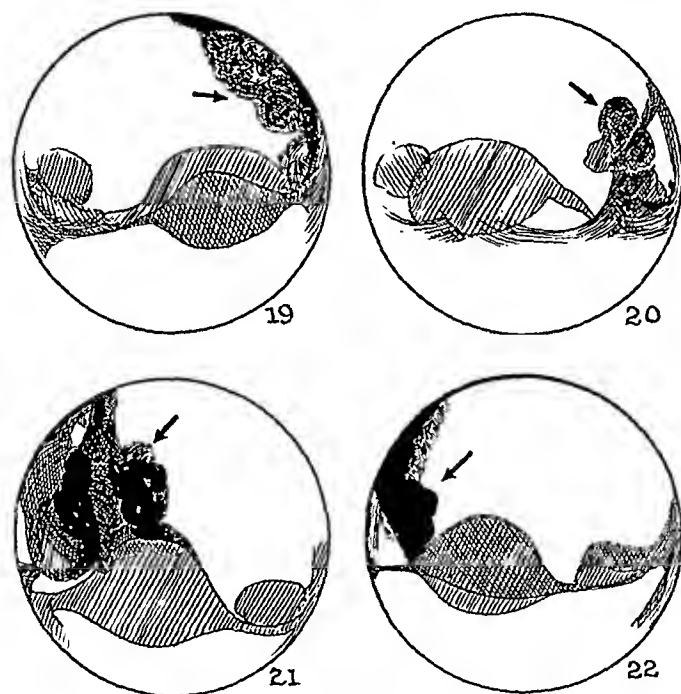


Fig. 4.—19, Left tubal pregnancy: unruptured; 20, left tubal pregnancy: unruptured; 21, right tubal pregnancy: partial tubal abortion; 22, right tubal pregnancy: unruptured.

mass on the x-ray film. In one of our cases, hysterosalpingography was used first and was of no diagnostic value alone, but when pneumoperitoneum was performed in addition, the adnexal mass was recognized as characteristic of a tubal mole (Fig. 5).

In this communication, 15 cases of early ectopic pregnancy are presented and illustrated (Figs. 1 to 4) in which gynecography was of distinct aid in diagnosis. Another group of cases is shown by way of contrast in which the symptoms were suggestive of ectopic pregnancy and in which the evidence from the x-ray film was sufficient to rule out the diagnosis of ectopic pregnancy. It is just as true of x-ray as of other diagnostic methods, that one must evaluate the findings in the light of

symptoms and other signs as well as correlating the history of the case in order to arrive at a correct diagnosis. In no case was entire dependence placed upon this one diagnostic procedure. In some, however, the gynecographic evidence was the *deciding* factor in determining treatment. That some conclusions drawn from the x-ray films were erroneous must be admitted, but these were errors of interpretation. In other instances, the films were of no diagnostic value whatsoever. In addition to aiding the positive diagnosis of ectopic pregnancy in some cases,

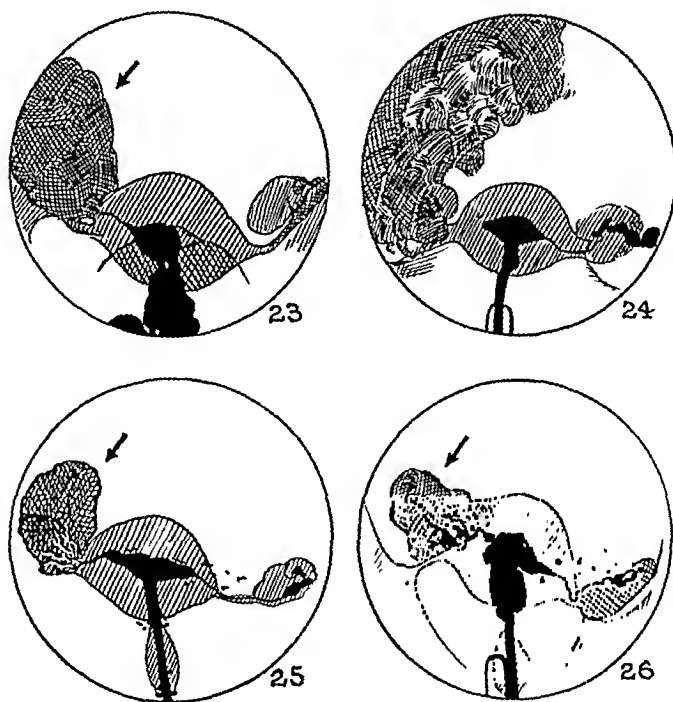


Fig. 5.—Combined gynecography. 23, Old unruptured tubal pregnancy: tubal mole; 24, unilateral inflammatory disease: simulating picture of tubal pregnancy on film; 25, right tubal mole: note dispersion of contrast medium upon entering blood clot in tube; 26, interstitial pregnancy right horn (mole): note dispersion of contrast medium in clot.

gynecography was instrumental in ruling out this diagnosis and at the same time, establishing that of another pelvic condition, i.e., intrauterine pregnancy, cystic ovary, etc. Hence, the method possesses both a positive and a negative value in the diagnosis of ectopic pregnancy.

CONCLUSIONS

1. Gynecography may be beneficially employed in the diagnosis of early and unruptured ectopic pregnancy.
2. Transabdominal pneumoperitoneum is more valuable, more informative, and less harmful than hysterosalpingography.
3. The two methods may be combined in selected cases with excellent results.

4. Unruptured tubal pregnancy can be shown on the pneumogram with sufficient clarity to serve as a positive means of diagnosis.

5. Gynecography has a negative value in the diagnosis of ectopic pregnancy in that it may show definitely intrauterine pregnancy with normal adnexa, ovarian cyst, and/or other lesions to account for the patient's symptoms, and thus rule out the presence of ectopic pregnancy.

I wish to acknowledge my gratitude to my colleagues on the gynecologic and roentgenologic services at Michael Reese Hospital for their permission to include their cases, and for their cooperation; and to Dr. Harold Laufman for the illustrations.

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310 SOUTH MICHIGAN AVENUE

THE USE OF UTERINE PACKS IMPREGNATED WITH SULFANILAMIDE*

A PRELIMINARY REPORT

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UTERINE packing as a tamponade in the puerperal uterus for the prevention of severe hemorrhage is an old procedure.

Leroux is credited¹ with first inventing the uterine tamponade in 1776, but Dührssen popularized² its use in 1887. Plain sterile gauze, and gauze to which various chemicals have been added, with the hope that their bactericidal action might sterilize the uterine cavity, have been used extensively. The most popular sterilizing agents in the uterine pack are iodoform, iodine, lysol, and hexylresorcinol, favored by various writers. DeLee¹ advocates 0.5 per cent lysol packing; Dührssen was the first to suggest² the use of iodoform gauze and has since had many followers, while Torpin³ feels that hexylresorcinol solution is an excellent bactericide in a uterine pack; Beck,⁴ however, suggests the use of moist sterile packing with no chemical bactericide, and Stander² prefers plain, sterilized gauze to that impregnated with iodoform or other antiseptics.

Various means of introducing the pack within the uterine cavity have been suggested by numerous operators.

Holmes,⁵ in 1902, introduced a mechanical uterine packer by means of which the uterus could be snugly packed. Torpin³ has recently modified the Holmes packer so that a larger quantity of gauze may be stored in a mechanical reservoir, and also various forms of liquid antiseptics may be added at the time of packing. DeLee¹ used the uterine dressing forceps, while Beck⁴ and Schumann⁶ stress the manual method of packing.

The sole purpose of the uterine pack is to control hemorrhage when all other means have failed to check uterine bleeding. It is not the purpose of this paper to discuss the use of uterine packing in any but post-partum bleeding. It is in the atonic uterus that the tamponade acts most effectively and dramatically. Its action is twofold in that it exerts pressure upon the bleeding vessels, as well as mechanically stimulates the uterus to vigorous contractions. The majority of authorities concede that in the atonic uterus, after such measures as

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The sulfanilamide used in this study was generously supplied through the courtesy of Eli Lilly and Company.

massage of the organ, exhibition of pituitary extract, and intravenous use of ergonovine have failed to control post-partum or post-abortion hemorrhage, no time should be lost and the uterus should be packed promptly.

Schumann⁶ admonishes haste in packing and advocates not waiting until signs and symptoms of acute anemia appear. Dorsett⁷ believes that too late packing fails to control bleeding, because, after the patient has lost a large quantity of blood, the uterus will not contract properly on account of atonic musculature and marked anemia; he therefore urges packing the uterus at the first sign of abnormal bleeding. Torpin⁸ states that the routine use of pituitrin and ergonovine is insufficient, since in his experience in a series of 200 cases in labor there was sufficient bleeding to be classed as post-partum hemorrhage; of this series 11 cases required uterine packing, notwithstanding the routine use of pituitrin and ergonovine. It is generally agreed that any amount of blood in excess of 500 c.c. lost at the time of delivery is considered post-partum hemorrhage.

A number of factors influence the likelihood of abnormal post-partum bleeding.

Davis⁸ considers improper conduct of the third stage of labor the most common etiologic factor in hemorrhage. He also thinks prolonged anesthesia and analgesia produce a marked lack of uterine tone and motility, thereby increasing the hazards in the third stage of labor. Long labors are a marked factor, as well as unusual operative interventions like version and extraction, difficult forceps deliveries, etc. He cautions that packing the uterus includes a considerable hazard of infection in the invasion of the uterus, but that delay in packing involves an even greater hazard because of the continuing blood loss.

Trauma and hemorrhage within the uterine cavity are the two chief predisposing factors in puerperal sepsis. No matter with what gentleness the pack is introduced into the endometrial cavity, there is certain to be a large amount of definite injury to the compact layer of the decidua. To understand better the damage produced by the traumatic invasion of the uterus by a foreign object, it may be well to describe the appearance of the uterus at the completion of the third stage of labor.

According to Watson,⁹ "The lining of the uterus is a continuous raw surface, more or less shaggy, incident to the separation of the decidua through the spongy layer. At the placental site, thrombi project to the large venous sinuses, giving this area a roughly elevated appearance. While some of the sinuses are occluded, some of them remain open, excessive bleeding from them being controlled by firm contraction of the uterine wall. In the course of the first week of the puerperium, a necrosis occurs in the superficial layers of the decidua, and this necrotic tissue is cast off with the lochial discharge, while active proliferation of the cells goes on in the deeper part, next to the uterine muscle, to form

the new mucosa." Thus, the whole lining of the uterus is simply a granulating surgical wound.

It is therefore easy to understand that any organisms present find an ideal nidus for their growth during the early stage of this "casting off and granulating process."

Watson⁹ further states, "Organisms are present in abundance in the superficial necrotic tissue, in the thrombi, and in any retained pieces of placenta or membrane. Underneath this layer is the remains of the decidua compacta, and in it an active reaction is taking place, being crowded with leukocytes. There is some edema, and thus a barrier zone is set up which prevents an extension of the organisms to the deeper levels."

In other words, this area is nature's first line of defense against infection, and if this protective barrier is not broken through, or removed by a process which may denude it, infection will be halted here and will not be spread further through the lymphatics or blood stream. Often, after removal of the uterine pack, bits of tissue were found scattered over the surface of the pack material. Suspicion that this tissue was composed of fetal and/or maternal membranous elements led to microscopic examination.

We have been able to show pieces of decidua and placenta embedded within the meshes of the gauze when the uterine pack was removed (Fig. 1). This protective zone had thus been loosened and carried away on the pack by a curettage-like action. The most dangerous form of treatment as far as infection is concerned is to curette the puerperal uterus. The pack usually is removed in from forty-eight to seventy-two hours after its introduction, and at this particular time, as shown by Armstrong and Burt-White¹⁰ and others, the uterus is teeming with organisms. Inasmuch as nature's barrier against infection is undoubtedly removed at least partially at the time the pack is withdrawn, it would seem reasonable to wish for some agent that might curb the pathogenic action of the existing organisms by its bacteriostatic action.

It has been long recognized that the introduction of any foreign object into the uterine cavity, immediately after the third stage of labor, increases the incidence of puerperal infection. For this reason various types of antiseptics have been employed in uterine packs with the hope that the action of the chemical, through its bactericidal action, would diminish the incidence of sepsis. In the experience of the senior author (H. E. A.), both plain sterile gauze and iodoform have been used to control bleeding and on occasion severe puerperal infection has followed removal of the pack. For that reason it was thought advisable, because of the bacteriostatic action of sulfanilamide, to attempt to impregnate gauze with this drug and to study experimentally its clinical action upon patients as well as its action upon the organisms within the uterine cavity.

The idea of using sulfanilamide for its bacteriostatic action in surgical wounds was first suggested by Jensen, Johnsrud and Nelson¹¹ in their report of a series of 39 compound fractures and 2 compound dislocations treated by local implantation of sulfanilamide. After completion of meticulous debridement, crystalline sulfanilamide (5 to 15 Gm.) was introduced into the wound, which was then closed with interrupted silk sutures. In this series there was no instance of primary wound infection, a much better record than would ordinarily be expected in a series of contaminated fractures. Since then, numerous articles have been published concerning the beneficial action of sulfanilamide in many types of surgical wounds.

SULFANILAMIDE IMPREGNATED GAUZE PACKS

The length of the pack used in this experimental study was four and one-half feet. We are fully aware that this is an insufficient length completely to pack an atonic uterus for hemorrhage; however, in this series there were only four instances of atonic uterus; therefore, four



Fig. 1.—Material obtained from within meshes of uterine pack, showing marked polynuclear infiltration, decidua cells, and large amount of chorionic villi.

and one-half feet were of sufficient length to pack completely the tonic uterus. The original thirty-six inch wide plain gauze is folded into 16 complete folds so that the width of the strip as it is inserted into the uterus is $2\frac{1}{2}$ inches, the selva edge being on the inside. Inasmuch as sulfanilamide is so little soluble in water, we found it best to soak the roll of gauze in water and wring out the excess moisture to the point that no water would drip. The pack was then opened and placed upon a flat surface, as shown in Fig. 2, and the contents of two-five gram sterile ampoules of sulfanilamide were distributed equally and thoroughly throughout the surface of the moist pack; the sulfanilamide was then rubbed into the meshes of the gauze so there was an even distribution throughout the length as well as the width of the pack. A small cotton ball measuring about 2 inches by $1\frac{1}{2}$ inches, to which a small piece of black linen thread had been tied for identification (Fig. 3), was then placed within the inner folds of the gauze, about nine inches from the end of the pack that would be placed nearest the fundus of the uterus, in such a position that only two layers of gauze separated the ball from the uterine cavity. The purpose of the cotton ball is to obtain

intrauterine cultures, and will be described more fully later. For identification, a numbered metal tag was attached by a string to the other end of the gauze pack. The pack was then rolled upon itself, starting with the tag end first, so that it would be ready to be inserted into the uterus when unrolled. It was then sterilized by the autoclave at 255° F. for thirty minutes under 20 pounds of pressure.

A pack similar to the one described above, with the exception that sulfanilamide was not added, was used as a control. Iodoform gauze packing was also used and made up in a similar manner, with 10 per cent iodoform and a cotton ball encased within its meshes. The total number

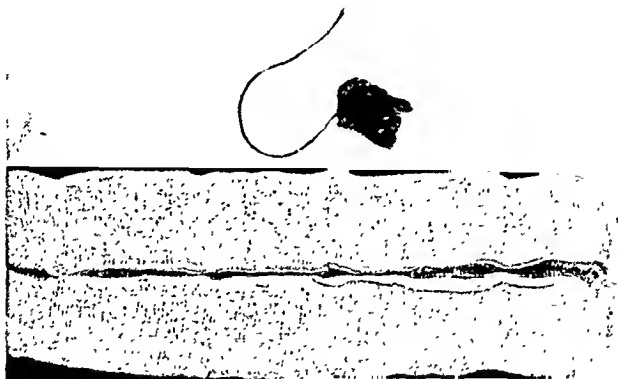


Fig. 2.—Moistened pack ready for impregnation with sulfanilamide powder. Cotton ball not inserted until after sulfanilamide is thoroughly distributed through pack.

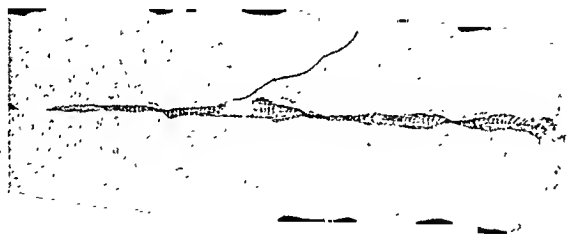


Fig. 3.—Position of cotton ball as inserted within folds of gauze, also its location with regard to the end which is inserted into the fundus.

of packs used in this study was 80. However, the first 10 were not checked by intrauterine cultures and for that reason tabulation of clinical results is computed on only 70. Of these, 37 were sulfanilamide packs, 27 plain packs, and 6 iodoform packs.

METHOD OF INTRODUCTION INTO THE UTERUS

The patient's legs were supported by stirrups. In each case in this series the following technique of introduction of the intrauterine pack was adhered to:

After the third stage of labor an anterior and posterior vaginal speculum was introduced and held as a retractor by an assistant. A ring

forceps was used to grasp both the anterior and posterior lips of the cervix, and by gentle traction the cervix was pulled down into the neighborhood of the vaginal introitus. The anterior speculum was then removed, but the posterior speculum was left in place to protect the pack from touching the anus. The pack was grasped by another ring forceps



Fig. 4.—Pack rolled, showing numbered metal tag. Actually the tag end is rolled up first in order that the opposite end containing the cotton ball may be inserted in the region of the uterine fundus.

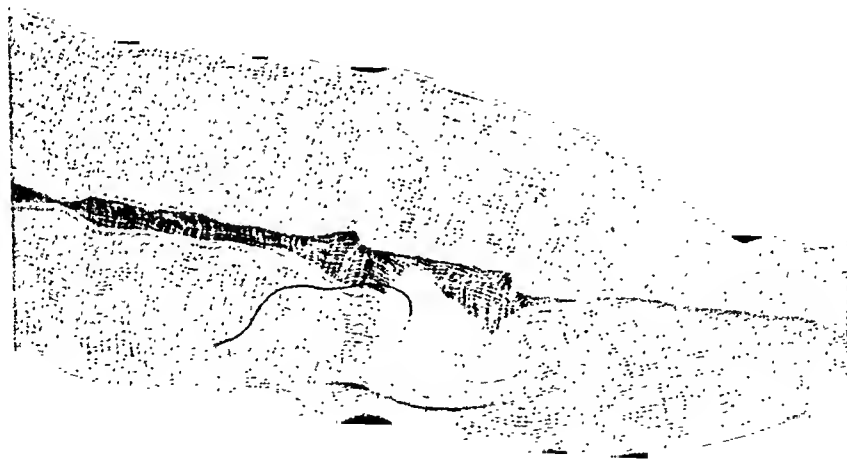


Fig. 5.—Showing the folds of the pack open in preparation to removing the cotton ball with the hemostat.

and packed snugly into the uterine cavity, after the free hand of the operator had firmly grasped the uterus through the abdominal wall, in order to steady the uterus from above and thereby discourage any tendency toward perforation. The entire pack was inserted into the uterine cavity and the string with the metal tag was left hanging

through the cervix and into the vaginal canal. Of course, knowledge of the direction of the cervical and uterine passage facilitates greatly the ease with which the uterus is packed. We found more difficulty in inserting a pack into the tonic uterus than into the relaxed bleeding uterus; the difficulty, of course, was produced by the pressure of the tone of the uterine wall. Usually, when the pack is within the uterine cavity, the patient complains of malaise, with or without low grade fever at times. It was not uncommon to have chills accompanying this fever within a few hours after the pack was inserted, and early in our series we removed two or three packs, but we subsequently found that the fever was not necessarily a dangerous sign. Less fever was also noted when the pack remained completely within the uterine corpus than if it had slipped down and had obstructed the cervix. In no case in this series was a pack used if the patient was frankly or potentially infected before insertion of the pack.

REMOVAL OF THE PACK

The average length of time that packs were allowed to remain in the uterus was as follows: Sulfanilamide 54½ hours; plain 43 hours, and iodoform 42½ hours. To remove the pack, the examiner's hand was encased in a sterile rubber glove, the first two fingers were introduced into the vagina, and the metal tag was firmly grasped. It was noted at this time whether any of the pack had been expelled into the vagina or not. Gentle traction was then made upon the pack and a minute or two consumed in removing its entire length. If, for any reason, there was difficulty in withdrawing the pack, the operation was stopped for a minute or so, then again resumed so that as much as five minutes was consumed at times in the removal of the pack. When the piece of black thread came into view, the edge of the pack was grasped by a sterile hemostat and the folds of the pack were opened (Fig. 4). From the cotton ball, grasped by another sterile hemostat, a small portion was excised by a pair of sterile scissors. This small excised portion of the cotton ball was then streaked over a blood agar plate and sent to the laboratory.

MORBIDITY

With morbidity represented by a temperature of 100.4° F. or over, it was interesting to note the following uncorrected morbidity. In the plain pack there was 72 per cent, in the sulfanilamide 38 per cent, and in the iodoform 20 per cent. In the sulfanilamide group, one patient had a severe paronychia during the first five post-partum days, and ran a temperature of 102° F. Another patient had acute sinusitis, with a temperature of 104° F. following delivery: the third was thought to have an acute appendicitis, but instead, in the region of the infundibulopelvic ligament, a hematoma was found, which in the operator's judgment, was not produced by the uterine pack. All rises of temperature of patients in the plain pack group, in our estimation, were directly due to the use of the packs. Two of these cases had a rather severe acute endometritis and the bacteriology in both showed nonhemolytic streptococci aerobically and *Staphylococci aureus* and *albus* on anaerobic culture. Both were treated with sulfathiazole and recovered.

One patient in the iodoform group on the second post-partum day showed a temperature of 100.4° F., which promptly subsided. The only organisms found both aerobically and anaerobically were nonvirulent diphtheroids.

RUPTURE OF MEMBRANES

The incidence of intrauterine infection is directly proportional to the time elapsing between the rupture of the membranes and the time of delivery; therefore, the ratio of infection upon this basis was greatly increased in the sulfanilamide group, because the length of time was ten hours and forty minutes; in the group of plain packs four hours and forty-two minutes; and in the iodoform group the time was twenty-four minutes.

TABLE I. TYPES OF DELIVERY

SULFANILAMIDE	PLAIN	ODOFORM
(a) 31.9% spontaneous	(a) 37% spontaneous	(a) 60% spontaneous
(b) 9.4% spontaneous with episiotomy	(b) 7.25% spontaneous with episiotomy	(b) 20% spontaneous with episiotomy
(c) 35.2% low forceps with episiotomy	(c) 33.5% low forceps with episiotomy	(c)
(d) 11.8% low forceps	(d) 18.75% low forceps	(d) 16% low forceps
(e) 5.8% frank breech with forceps to head	(e)	(e) 4% frank breech with forceps to head
(f) 5.8% forceps rotation posterior position	(f)	
	(g) 3.5% internal version and breech extraction	

BLOOD SULFANILAMIDE LEVELS

The purpose of this study was solely to note the bacteriostatic action of sulfanilamide within the uterine cavity, with no hope of obtaining a generalized action from the drug. However, we were curious to ascertain whether or not some of the drug was absorbed through the uterine mucosa, as we might expect, because of the nearness and abundance of the blood supply within the uterus. Blood sulfanilamide levels were therefore run on selected cases early in the series. This was soon discontinued because of the unanimity of results obtained on the blood levels.

TABLE II

Case 1, left in 53 hr.		
24 hr., 0.3 milligrams %		
48 hr., none		
Case 2, left in 52½ hr.		
4 hr., 8.8 milligrams % free	1.0 milligrams % total	
45 hr., 0.5 milligrams % free	1.3 milligrams % total	
Case 3, left in 49½ hr.		
23 hr., 3.1 milligrams % free	4.6 milligrams % total	
48 hr., 0.9 milligrams % free	2.5 milligrams % total	
Case 4, left in 52 hr.		
25 hr., 1.2 milligrams % free	2.3 milligrams % total	
48 hr., 0.5 milligrams % free	1.3 milligrams % total	
Case 5, left in 48 hr.		
6 hr., 1.3 milligrams % free	1.9 milligrams % total	
29 hr., 1.9 milligrams % free	2.3 milligrams % total	
48 hr., 1.4 milligrams % free	0 milligrams % total	
Case 6, left in 44 hr.		
3 hr., 1.7 milligrams % free	1.8 milligrams % total	
26 hr., 2.2 milligrams % free	4.7 milligrams % total	
46 hr., 2.0 milligrams % free	0 milligrams % total	

Case 7, left in 60 hr.		
34 hr.,	1.5 milligrams % free	2.5 milligrams % total
Case 8, left in 48 hr.		
21 hr.,	3.5 milligrams % free	6.1 milligrams % total
42 hr.,	3.6 milligrams % free	5.0 milligrams % total
Case 9, left in 54 hr.		
3½ hr.,	1.3 milligrams % free	1.8 milligrams % total
Case 10, left in 57 hr.		
30 hr.,	2.0 milligrams % free	
58 hr.,	0.3 milligrams % free	0.6 milligrams % total

ODOR

If the sulfanilamide pack had no therapeutic virtue other than removing vaginal odor, the use of sulfanilamide in a pack would be justified. Almost without exception in the sulfanilamide packs, there was no odor about the patient while the pack was in the uterus or at the time of withdrawal. However, the converse was true with the plain pack; in most instances the odor was very foul and was complained of by both the patient and nursing staff. The iodoform pack reeked of the characteristic odor of the drug, but at no time could a foul odor due to lochia be detected.

BACTERIOLOGY

Two types of media were employed for the cultivation of the organisms found in the cotton balls. The first, blood agar, was 10 per cent goat's blood in veal infusion agar. The second was Brewer's¹² medium. This is a pork infusion broth containing 0.05 per cent agar, 0.1 per cent sodium thioglycollate, and the indicator, methylene blue. The sodium thioglycollate is the active ingredient so far as maintaining anaerobic conditions are concerned.

Approximately the upper 1 to 2 cm. is aerobic, and here the methylene blue has a green color. Thus, it is possible to cultivate aerobic, microaerophilic or anaerobic organisms in this one liquid medium.

The cotton balls, which have been previously described, are particularly adaptable to such an investigation. They are small, of uniform size, and can be easily inserted or withdrawn. Being placed in the folds of the pack they provide as nearly as possible a true picture of the bacteriologic flora of the pack. Immediately following their removal they were streaked over the entire surface of a blood agar plate. They were then immersed in Brewer's medium and squeezed against the side of the tube so that the medium was sure to be inoculated. The cultures were then incubated at 37° C. for twenty-four hours. If no growth was present at this time they were observed at various intervals for one week and then discarded.

Table III shows the organisms found and the frequency with which they occurred in the three different packs.

TABLE III

ORGANISMS FOUND	PLAIN (27)		SULFANILAMIDE (37)		IODOFORM (6)	
	PLATE	BREWERS	PLATE	BREWERS	PLATE	BREWERS
No growth	2	—	15	2	—	—
Streptococcus (Nonhem.)	6	7	8	7	1	1
Streptococcus (Hem.)	4	4	1	—	1	2
<i>S. albus</i>	13	13	6	10	3	2
<i>S. aureus</i>	6	2	—	—	—	—
Diphtheroid (Nonvir.)	7	4	7	8	1	1
<i>E. coli</i> (Hem.)	2	2	—	—	1	2
<i>E. coli</i> (Nonhem.)	2	2	—	—	1	1
Anaerobic Staph.	—	2	—	3	—	—
Anaerobic Strep.	—	—	—	4	—	—
Spore former	5	2	—	—	—	—
<i>St. viridans</i>	—	—	1	1	—	—
<i>A. aerogenes</i>	—	—	—	—	1	1
<i>Sarcina lutea</i>	1	1	—	—	—	—
Unident. gram-negative rod	1	1	—	1	—	—

This table shows, in the sulfanilamide packs, bacteriologic flora markedly different from the flora of other packs. The sulfanilamide packs gave more blood agar plates with no growth and significantly showed a marked diminution in the growth of the hemolytic streptococcus aerobically, while no growth at all was obtained in the anaerobic culture. In addition, the *E. coli* (both hemolytic and nonhemolytic) and the spore formers were absent both aerobically and anaerobically. All these factors are in sharp contrast to bacteriologic findings for the plain and iodoform groups.

SUMMARY

1. Various types of uterine packing have been reviewed, either plain or impregnated with some chemical. Likewise, various means of introducing the pack within the uterus have been described.

2. The sole purpose of the uterine pack is to control bleeding in the atonic uterus after other means have been used as oxytocics.

3. Delay in the use of the uterine tamponade very often results in a fatality.

4. The introduction of any foreign object into the uterus increases the incidence of infection. The withdrawal of the uterine pack produces a curettage-like action at the time when the uterine cavity is teeming with bacteria.

5. The purpose of the use of sulfanilamide impregnated gauze packs is prophylactic against infection because of the bacteriostatic action of the drug at the site of contact with tissue.

6. The technique of impregnating the gauze pack with sulfanilamide is described and discussed.

7. The use of a small cotton ball, enmeshed within the meshes of the uterine pack, serves as a very satisfactory means of obtaining both aerobic and anaerobic intrauterine cultures.

8. In our judgment, grasping the anterior and posterior lips of the cervix with ring forceps, thereby bringing the cervix directly into view, and snugly introducing the gauze into the uterine cavity by means of a third ring forceps is the most acceptable manner of packing the uterus.

9. There is a general diminution in the number and kinds of bacteria in general, and of the hemolytic streptococci and *Staphylococcus aureus* in particular, when sulfanilamide is used to impregnate the intrauterine pack. Clinically, the plain pack, used as an intrauterine tamponade, increases morbidity above that of either the sulfanilamide or iodoform pack.

10. This preliminary series is small, from a bacteriologic standpoint, and a larger number of cases is desirable before definite conclusions are drawn. However, from the fact that sulfanilamide gives a much more sanitary pack, tends to decrease the bacterial flora, inhibits growth of hemolytic streptococci, and is absorbed to a limited degree into the blood stream, it seems advisable to use sulfanilamide packs in preference to either plain or iodoform, when indicated.

The blood sulfanilamide levels in this series were done under the direction of Dr. V. M. Wilder.

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DISCUSSION

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—Dührssen formulated the indications and the method for the introduction of uterovaginal tampons for post-partum hemorrhages in the mid eighties, but general acceptance of his advice by the American obstetricians was only realized early in this century. I, myself, employed tamponades from the very beginning of my practice. At first, we all used sterile gauze and quickly learned its value as a means of controlling hemorrhage, but appreciated also that the gauze must not only be sterile but must be, to a degree, definitely antiseptic. If the gauze were not impregnated with a germicide it became very foul before it was extracted, showing that saprophytes developed in the gauze, and there was evidently the possibility of a virulent infection developing from its use. Gauze saturated with a 1:10,000 bichloride solution or "washed" iodoform gauze produced similar results. Both of these chemicals were also decidedly objectionable in that they were readily absorbable poisons. After trying all kinds

of antiseptics, we found that a certain proprietary preparation was the most efficacious, but its expense for each tampon was prohibitive. A gauze wet with weak liquor cresolis compositus was distinctly valuable, as the drug was inexpensive and always available.

I would stress that saturation of a sterile gauze with an antiseptic solution is not a sufficient precaution. Other requirements are the following: the impregnated gauze must be sterilized in a permanent container (i.e., a quart wide mouth jar with a glass top); the antiseptic must not be decomposed by the high temperature of an autoclave; the drug shall not be of a potency or type poisonous to the woman; the gauze should be 12 feet long and 18 inches wide, the raw edge folded within the pleats and the strip finally not much more than two inches wide.

There are a number of variants in the technique of introducing the gauze, but even with the vagina widely opened by large specula and ring forceps applied to the anterior and posterior lips of the cervix, there is always an inherent danger that the gauze will scrape on the skin or mucosa. There is a further danger that the gauze as it passes over the cervical canal will so irritate the uterus to contract that the tamponade may be introduced only with difficulty, or even be prevented by the tightly retracted lower segmental ring. To obviate these difficulties and dangers I devised in 1899 a special tube sufficiently large to carry the ribbons of gauze 2 inches wide. For insertion of the instrument the tube had an obturator which could be removed after which, with an *introducer* the gauze was placed in situ. The great advantage of this tube was that the gauze only touched boiled surfaces from the moment of its exit from the glass container until it was in contact with the uterine mucosa.

If there be atony, the uterus should not be overpacked, for if the pack be too tight it will prevent retraction of the uterus. It must be appreciated that the pack serves a double purpose, namely to dam the bleeding vessels and to stimulate the uterus to contract and retract. The gauze should invariably be in one piece, and never be left more than twenty-four hours. If fearful of a recurrence of hemorrhage, be prepared to tampon again at the time the gauze is removed.

DR. H. CLOSE HESSELTINE, CHICAGO, ILL.—It takes, of course, quite a number of cases to work out the statistical advantages of a new procedure. Dr. Anderson found it necessary to use many normal patients to make this study, for in the usual course of events it would take a long time to have a sufficient number that had to be packed.

The need for packing in a properly managed case is very infrequent. Prior to the introduction of ergonovine, less than 1 per cent of the parturient patients on our service were treated by intrauterine pack. M. Edward Davis has a report in progress which indicates that the need for pack has now been reduced 90 per cent. This agrees in part with Dr. Diddle's paper earlier this morning.

In regard to the chemical substances used, the method of sterilizing the pack must be carefully considered, for overheating may cause the drug to change. Toxicity to the mother must be thought of, for one of our patients developed nephritis following the insertion of a pack moistened with one-half per cent lysol solution.

I would like to ask Dr. Anderson whether the patients had any irregularities in menstruation after the menstrual cycle was established. Probably there will be no special damage within the intrauterine cavity but one should investigate for such residual injury.

The question should be raised as to which one of the sulfonamides is most valuable (sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and sulfaguanidine). Sulfaguanidine is the most insoluble and has been used quite successfully in intestinal

surgery, and perhaps sulfaguanidine might be better in the uterus. Sulfadiazine appears more toxic than sulfathiazole and sulfathiazole is better tolerated than sulapyridine.

One should not rely upon the sulfonamides to correct one's techniques. The prolonged period during which the pack was left in the uterus by the writers may be criticized. We seldom leave a pack for more than eighteen hours.

DR. ANDERSON (closing).—The sulfanilamide pack on removal has absolutely no odor. For that reason alone the sulfanilamide pack would merit use instead of either the plain or iodoform pack.

We made some quantitative chemical tests to see whether the sulfanilamide was lost in the sterilization. We analyzed an impregnated pack chemically and found that, out of the 10 Gm. which were put in, there were returned some 8.5 to 9 Gm. of the drug.

With regard to possible later disturbances of menstruation, I have no information.

PREMATURE RUPTURE OF MEMBRANES*

A CLINICAL STUDY

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WHENEVER a pregnant patient is observed who is not in labor and in whom the amniotic sac has ruptured and the fluid has been lost, a problem concerning the most satisfactory management immediately presents itself. Because of a clinical interest in these patients with premature loss of fluid and in the associated conditions which may result from early rupture of membranes, we have reviewed a series of such cases in order to study the possible changes in uterine physiology, the effects of dry labor, and the results obtained by various methods of management.

MATERIAL

One thousand histories of women delivered at the Chicago Lying-in Hospital in whom the membranes ruptured prior to the onset of labor were obtained. They were consecutive and unselected except for this one requirement. Chemical tests were not usually used to determine or confirm the diagnosis of premature rupture and the clinical diagnosis plus the confirmation of previous rupture at the time of delivery were used as the criteria. Because of the elimination of questionable cases as far as possible, an incidence figure for premature rupture is not attempted.

The scatter chart (Fig. 1) indicates the case distribution of the 1,000 patients in regard to the period of gestation in weeks and the latent

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

period in hours before the onset of labor, as well as fetal mortality which was associated. The latter are circled in black, those with 2 black circles indicating dead infants having evidence of lung infection at autopsy.

Of these patients, 536 were primiparas and 464 were multiparas; 71 had artificial rupture of membranes, and in the remainder rupture occurred spontaneously. One hundred and eighty-two patients had castor oil, quinine, pituitrin, bag, or a combination of these inductions superimposed on the already ruptured membranes. Although these compound inductions confuse the physiologic picture, they were included because of their possible clinical importance. Subsequent tables will show the analyses of these cases.

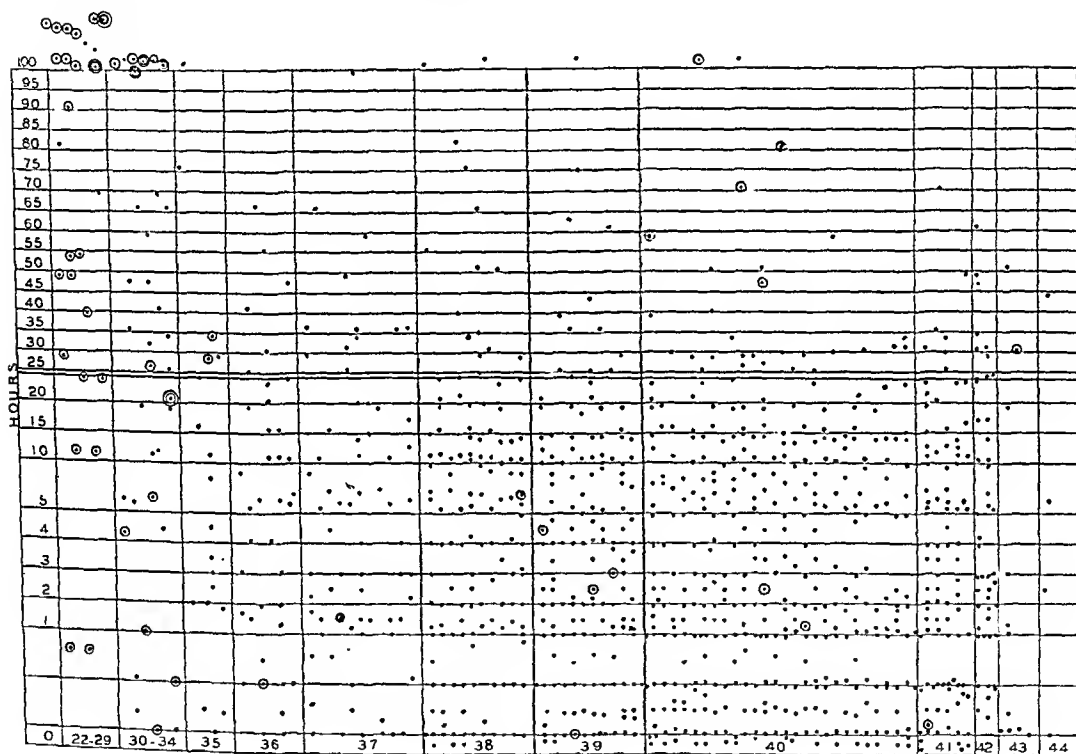


Fig. 1.

No particular effort has been made in this series to study the etiologic factors for the premature rupture. Factors which may possibly be significant, such as the presentation of the fetus and abnormal states in the mother, are shown in Tables I and II. Where available, the incidence of their occurrence in large hospital statistics is shown for comparison.

In this series 91.5 per cent of the cases had the vertex presenting in comparison with 94.95 per cent occurrence in the Chicago Lying-in Hospital series. There were proportionately more occiput posteriors (9.64 to 6.58 per cent) and breeches (6.5 to 4.2 per cent) while the incidence

TABLE I. POSSIBLE RELEVANT COMPLICATIONS

	NUMBER	PER CENT	INCIDENCE OF OCCURRENCE IN HOSPITALS C.L.I.H.
Toxemia	122	12.2	10.17
Contracted pelvis	35	3.5	3.65 (Mengert)
Placenta previa	4	0.4	0.9
Low lying placenta	6	0.6	
Abruptio placentae	7	0.7	7.7
Previous cesarean section	5	16.6	11.8 of 1000 c.s.
Heart disease	14	1.4	1.0+
Diabetes	6	0.6	0.10
Prolapsed cord	5	0.5	0.8 (Schiller)
Artificial rupture	71	7.1	—
Bag induction	20	2.0	—
Medical induction	162	16.2	—
Pyelitis	3	0.3	1.1
Polyhydramnios	3	0.3	0.34
Fibroids	2	0.2	12.0
Latent syphilis	7	0.7	2.5 (Williams)
Arrested tuberculosis	5	0.5	0.37
Hyperthyroid	1	0.1	0.07
Post-partum hemorrhage	16	1.6	2.5
Intra-partum infection	1	0.1	—

TABLE II. PRESENTATION—POSITION—MULTIPLE PREGNANCIES

	NO.	PER CENT	HOSPITAL
O.L.T.	279	27.46	94.95 (DeLee 35,179)
O.D.T.	214	21.06	
O.L.A.	147	14.46	6.58
O.D.P.	98	9.64	
O.L.P.	83	8.17	5.92
O.D.A.	78	7.67	
Breech	66	6.50	4.20
[Twins]	12	1.18	1.18 { 1934-1940 }
			{ 15,957 cases }
Compound	3	0.29	
Transverse	2	0.19	0.45
Face and Brow	2	0.19	0.45
Vertex (not indicated)	16		

of twins was the same (1.18 per cent), and that of transverses and deflexed attitudes was slightly less (0.19 to 0.45 per cent each). The incidence of contracted pelvis, toxemias, placenta previa, premature detachment of the placenta, heart disease, and diabetes (see Table II) cannot be interpreted as being significant. Cesarean sections, prolapsed cords, and inductions of labor will be discussed elsewhere. Post-partum hemorrhages (500 c.c. and more) occurred in 1.6 per cent of the patients, which is slightly less than the hospital average.

Polyhydramnion was diagnosed only three times in this series and in two of these cases normal infants were delivered. In view of the relatively high incidence of malformations and erythroblastosis in this series, it seems possible that undiagnosed polyhydramnion has occurred and has been a factor in the early loss of the amniotic fluid.

Prolapse of the umbilical cord occurred five times and a partial prolapse once. The partial prolapse occurred at term and was associated with a breech presentation. A vaginal Voorhees bag was inserted and a living infant was delivered. One prolapse took place following spontaneous rupture of the membranes at thirty-seven weeks. The infant was in an O.L.A. position and was delivered alive but died two days later of pneumonia. The cord of a second twin prolapsed after delivery of the first twin at thirty-six weeks' gestation. A living infant was delivered by version and extraction. Two prolapses with fatal results occurred at thirty-three weeks; one of these took place when the membranes were artificially ruptured for treatment of a partial placenta previa, and the other occurred when the cord and an arm both prolapsed

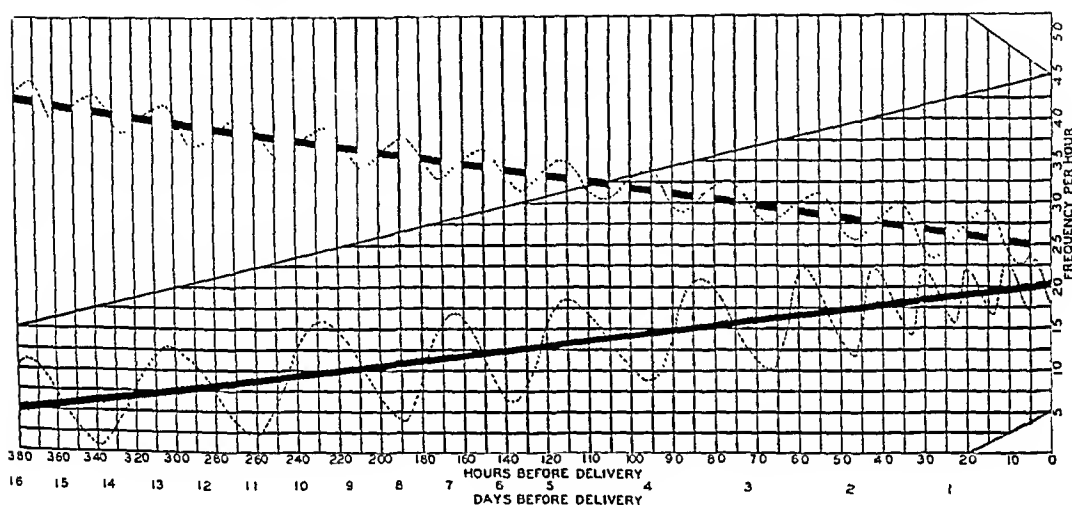


Fig. 2.

following spontaneous rupture, the infant being in a transverse presentation. In the sixth case spontaneous rupture occurred at twenty-eight weeks. The infant died, and a craniotomy was done to complete the delivery.

Thus all cases of complete prolapse occurred in relation to rupture of membranes prior to the expected termination of pregnancy, and none were found at term. For the series, the incidence of complete prolapse is 0.5 per cent.

UTERINE IRRITABILITY

It is well known that at different periods of gestation the uterus will respond differently to a given stimulus, and that there is a relative lack of irritability before term, causing increased difficulty in the induction of labor prior to the expected termination of pregnancy.

At the Chicago Lying-in Hospital, Dr. Con Fenning of the University of Utah made a careful study of over 500 patients, using external hysterographic methods, in an effort to determine the normal action of

human uterine musculature in vivo. Although this work is as yet unpublished, he has kindly given permission to use some of his illustrations and figures.

Fig. 2 shows the uterine activity in terms of frequency of contractions per hour for both small and large contractions. Note that as the time of delivery approaches, there is an increasing frequency of large contractions and a decreasing frequency of small contractions. He found, too, that after the membranes ruptured prematurely, there was an increase in the length and height of the contraction phase. This corresponds to the clinical observation that after the membranes rupture, labor pains become stronger; therefore, by rupturing the membranes at any given point, a shortening of the period that elapses before delivery occurs would be expected. The superimposition of oxytocic agents or

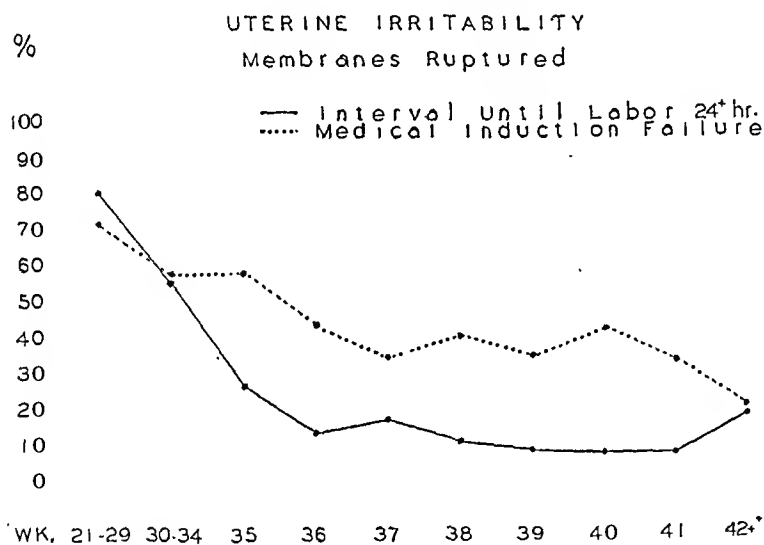


Fig. 3.

bags may further modify the action of the uterus, but the extent of alteration does not seem to have been satisfactorily demonstrated. The use of external hysterography definitely demonstrates that pituitrin can cause the uterus to contract at any phase of pregnancy which is sufficiently advanced to make possible the use of such an instrument; this does not mean, however, that labor will necessarily ensue.

The data regarding the latent periods between the time of rupture and the onset of painful contractions are shown for the 1,000 cases included in the present study in Table III. At term only 4.7 per cent of the primiparas and 7.3 per cent of the multiparas had latent periods of thirty hours or more. The actual length of these intervals is more apparent in Fig. 1. For instance, at 22 to 29 weeks, almost half (42.3 per cent) of the patients had latent periods of over one hundred hours with individual cases in this group running up to sixty-seven days. In the

TABLE III. LATENT PERIOD

WEEKS	PARTY	NUMBER	MEANS IN HOURS												FENNING RUPT. MEMB.		FENNING "NORMAL"			
			0-5 HR.		5-10 HR.		10-15 HR.		15-20 HR.		20-25 HR.		25-30 HR.		30+ HR.		NO.	%	NO.	%
			NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%				
22-29	Primip.	10	1	10.0	0	0	0	0	0	0	0	0	0	0	2	20.0	0	0	7	70.0
	Multip.	12	0	0	0	0	1	8.3	0	0	1	8.3	1	8.3	1	8.3	1	8.3	9	75.0
30-34	Primip.	20	8	40.0	0	0	1	5.0	1	5.0	1	5.0	1	5.0	1	5.0	1	5.0	8	40.0
	Multip.	13	7	53.8	5	38.5	1	7.7	0	0	0	0	0	0	0	0	0	0	0	0
35-37	Primip.	62	33	53.2	6	9.7	4	6.4	4	6.4	3	4.8	1	1.6	3	4.8	1	1.6	8	13.0
	Multip.	57	24	42.1	10	17.5	5	8.8	3	5.3	4	7.0	1	1.8	4	7.0	1	1.8	10	17.5
38-44	Primip.	444	276	62.2	50	11.3	49	11.0	27	6.1	10	2.3	11	2.5	10	2.3	11	2.5	21	4.7
	Multip.	382	234	72.3	51	13.3	26	6.8	15	3.9	16	4.2	12	3.1	16	4.2	12	3.1	28	7.3
	Total	464																		
38-44	Primip. 0-85 hr.	442	7.76		7.04 ^s		FENNING RUPT. MEMB.		FENNING "NORMAL"		FENNING "NORMAL"		FENNING "NORMAL"		FENNING "NORMAL"		FENNING "NORMAL"		FENNING "NORMAL"	
	Multip. 0-85 hr.	380	9.38		8.07 induction		20.8		7.4		12.0		7.9		7.9		7.9		7.9	

group at term nearly 80 per cent of the patients were in labor within ten hours, 62.2 per cent of the primiparas and 72.3 per cent of the multiparas being in painful labor within five hours or less. It can be demonstrated with the hysterograph or by careful palpation that most of the patients going into labor soon after rupture of membranes are already having regular uterine contractions at the time membranes rupture even though they do not as yet feel pain. To give oxytocic agents to such patients could be dangerous. Patients in the entire groups that had more than a fifteen-hour latent period were unusual, and in these we would perhaps be justified in stimulating labor. We could at the same time better evaluate the usefulness of the induction.

The latent periods, both with and without the induced eases, compared with as yet unpublished figures of Dr. Fenning are shown at the bottom of Table III. The mean interval rises when the eases with medical induction of labor are added because more with prolonged latent periods are thus included. However, one would expect more dramatic results if the inductions had been highly successful in shortening the latent periods.

The irritability of the uterus in this series of eases, is shown more graphically in Fig. 3, the solid line representing the percentages of patients at different periods of gestation having latent periods of over twenty-four hours. The dotted line represents the percentages of failed medical inductions. This chart indicates the chances that any given patient with ruptured membranes will have of going for twenty-four hours without labor pains, and the chance there will be of not getting a satisfactory result following attempted induction with castor oil and quinine or pituitrin.

DURATION OF FIRST STAGE

The data pertaining to the length of the first stage of labor are shown in Table IV. Those patients that had operative intervention before complete dilatation of the cervix have been partially eliminated because of the inability to tell how long dilatation would have taken and when delivery would otherwise have occurred. The excluded eases include principally those with delivery by cesarean section and those in whom actual labor was never established. Those that had Dührssen's incisions were not excluded and appear largely in the group over thirty hours, thus not significantly altering the results. Because of the fact that the second and third stages are less pertinent to the discussion and because of possible modification of the figures as a result of the high percentage of operative deliveries and the use of ergonovine with delivery of the shoulders, no attempt has been made to evaluate or discuss this part of labor, except as noted under "Treatment."

At term we found that 76.3 per cent of the primiparas were fully dilated in less than fifteen hours and that 6 per cent required more than

TABLE IV. DURATION OF FIRST STAGE

WEEKS	PARITY	NUMBER	MEANS IN HOURS															
			0-5 HR.		5-10 HR.		10-15 HR.		15-20 HR.		20-25 HR.		25-30 HR.		30+ HR.			
			NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%		
22-29	Primip.	8	2	25.0	4	50.0	1	12.5	0	0	1	12.5	0	0	0	0		
	Multip.	11	7	63.6	3	21.3	1	9.1	0	0	0	0	0	0	0	0		
30-34	Primip.	18	5	27.8	2	11.1	6	33.3	3	16.7	0	0	0	0	1	5.6		
	Multip.	13	1	7.7	2	15.3	0	0	1	7.7	0	0	0	0	8	61.0		
35-37	Primip.	61	16	26.7	19	31.1	12	19.7	6	9.8	6	9.8	0	0	2	3.3		
	Multip.	55	38	44.9	8	9.5	6	7.1	1	1.2	0	0	1	1.2	2	2.4		
38-44	Primip.	433	115	26.6	138	31.9	77	17.8	41	9.5	21	4.8	15	3.5	26	6.0		
	Multip.	362	223	61.6	98	27.0	20	5.5	9	2.5	4	1.1	1	0.3	7	1.9		
Total		520																
MEANS IN HOURS																		
38-44	Primip. 0-80 hr. Multip. 0-80 hr.	433 362	SERIES		FENNING—MEMB. RUPT.						FENNING—NORMAL							
			11.52 { 11.1 5.77 { 5.4 induction }															
																	17.0 11.5	

thirty hours. At term 88.6 per cent of the multiparas were dilated in ten hours or less and only 1.9 per cent were prolonged to more than thirty hours.

For comparison with Fenning's figures, the means in hours of the first stage, both with and without induction, are shown at the bottom of Table IV. As noted, Fenning's figures are calculated for three stages whereas those given for the present series are calculated for the first stage only.

We can deduce from Table IV that once labor is established, it proceeds with about uniform efficiency regardless of the period of gestation. However for some unexplained reason, 8 of the 13 multiparas in the thirty to thirty-four-week group had a first stage of over thirty hours.

TREATMENT

All patients with ruptured membranes are advised to enter the hospital even though pains have not started. It is generally believed that these patients will go into labor spontaneously within a few hours even if untreated, but that if labor does not begin the hazard to the mother and infant from infection increases in proportion to the lengthening of the time between the rupture of membranes and delivery.

Such patients are kept at bed rest in order to aid in preventing vaginal contamination and to prevent cord prolapse. The most critical time in regard to the latter would seem to be immediately after the rupture of membranes. This, however, usually occurs outside of the hospital and considerable activity on the part of the patient is necessary before admission is possible. Following admission, with patients who are otherwise normal, a general physical examination including a rectal examination is done. After a period of observation, a medical induction by means of castor oil and quinine or pituitrin is attempted if the patient does not go into labor spontaneously. If this treatment fails, further procedures depend on indications present in the individual case.

As previously noted, 182 patients in this series had inductions of labor. This group received 80 castor oil and quinine inductions, 119 pituitrin and 7 bag inductions (13 more Voorhees' bags were used but not for the sole purpose of induction). The percentage of failures among the combined castor oil and quinine and pituitrin inductions have been indicated in Fig. 3.

Of the 20 instances among the 1,000 cases in which Voorhees' bags were utilized, it was used for the single purpose of induction in 7 cases. Pituitrin inductions were simultaneously used so that it is difficult to evaluate the value of a bag induction alone. In two cases there was failure of induction and a craniotomy on a dead baby was done in one and a vaginal hysterotomy in the other.

The methods by which these patients were delivered is shown in Table V. Over half (55.5 per cent) were delivered naturally. The in-

TABLE V

MANAGEMENT	NUMBER	PER CENT	HOSPITAL	
Natural	535	53.5	59.21	C.L.I.H 15,957 cases 1934-1940
Low forceps	323	32.3	26.36	
Midforceps	38	3.8	3.81	
High forceps	1	0.1	-	
Version	11	1.1	0.98	
Dührssen's incisions	18	1.8	1.11	
Breech extraction	39	3.9	-	
Forceps aftercoming head	25	2.5	-	13,022 cases 1935-1940
Cesarean section	28	2.8	4.65	
Vaginal hysterotomy	1	2.1	0.03	
Radical cesarean section	2	0.2	0.28	
Craniotomy	8	0.8	0.38	
Manual removal placenta	34	3.4		

cidence of versions, midforceps, Dührssen's incisions, and radical cesarean sections is approximately the same as for the hospital generally, but an increase is noted in the incidence of outlet forceps and a decrease in the percentage of cesarean section. Probably the increase in the number of low forceps can be accounted for because of an increased concern for the mother or baby and a wish to terminate the labor as quickly as possible.

Seven of the 30 cesarean sections were performed on patients that had been, in general, under observation as outlined previously. One of the recognized contraindications to cesarean section at the Chicago Lying-in Hospital is the presence of ruptured membranes for over twenty-four hours, unless a radical section is to be done. These 7 patients had borderline indications for section, and if a trial of labor had been possible, this would have been given. However under the circumstances it was considered too hazardous to wait and the operation was performed immediately.

One of the radical cesarean sections was done because of prolonged membrane rupture, dystocia, and intrapartum infection. In the other inertia followed artificial rupture of the membranes and failed medical inductions which were undertaken because of a low-lying placenta. The latter was further indicated by the fact that sterilization had been previously advised.

In the entire group of 28 laparotomies, the operation was performed in 21 after the membranes had been ruptured for over six hours. Seven, or 25 per cent, became febrile; whereas the general morbidity rate in this hospital for cesarean section is 42.9 per cent.

MATERNAL MORBIDITY

The morbidity standard used at the Chicago Lying-in Hospital is that of the American Committee on Maternal Welfare, which considers all

TABLE VI. PUERPERIUM

MATERNAL MORBIDITY	NUMBER	PER CENT		C. L. I. HOSPITAL RATE
Total morbidity for this series	63	6.3		7.7 1932-1940
Nonoperative morbidity Membranes rupt 24 hr.+	8	6.4		
Morbidity etiology		CASES	SERIES	
Endometritis	28	44.4	2.8	
Wound infection	13	20.6	1.3	
Pyelitis	6	9.5	0.6	
Upper resp. infection	6	9.5	0.6	
Mastitis	4	6.0	0.4	
Thrombophlebitis	3	4.7	0.3	
Pulmonary embolism	2	3.2	0.2	
Maternal mortality	1	0.1		1.75
Etiology: Eclampsia				

patients as morbid who have a temperature of 38° C. or above on more than one day after delivery, excluding the first twenty-four hours. The morbidity in this series, the general hospital morbidity, and the separation of the febrile cases by causes are shown in Table VI. Of the total 63 cases which were febrile in the post-partum period, 41, or 65 per cent, occurred in patients that had had some type of operative procedure. Among the 80 nonoperative cases in this series with membranes ruptured over twenty-four hours, 6.4 per cent were febrile. This varies but slightly from the 6.3 per cent morbidity for the total 1,000 cases, and it is also less than the general hospital morbidity rate of 7.7 per cent.

There were 78 patients who had ruptured membranes plus a first stage totaling forty-eight hours and over. Of these, 8, or 10.25 per cent, became febrile. In 2 of the 8 cases, the cause of fever was extragenital; 1 patient had had Dührssen's incisions, and in 5 Voorhees' bags had been inserted.

A diagnosis of intrapartum infection was made prior to delivery on 6 of these patients. Two were at term. One was delivered by a successful radical cesarean section, and in the other the infection subsided in a few days following delivery by a craniotomy on a dead baby. (The baby showed intrauterine pneumonia.) The other two intrapartum infections followed unsuccessful attempts to induce labor with pituitrin and Voorhees' bags at twenty-four and thirty-three weeks' gestation, respectively. A craniotomy was done to deliver one patient and a vaginal hysterotomy to deliver the other. One developed septicemia and the other a pelvic thrombophlebitis with pulmonary infarction. Both patients recovered after a prolonged convalescence.

In retrospect, it is believed that abdominal hysterotomy would have been the method of choice in the two last cases. The high degree of uterine inertia which has been demonstrated at these periods of gestation should cause us to anticipate failure of induction in a high percentage of cases.

In addition there were two patients who had an elevation of temperature during labor who were afebrile after delivery.

MATERNAL MORTALITY

One patient in this series, who had had no prenatal care, died. She entered the hospital in coma, with premature detachment of the placenta and anuria. The membranes were ruptured artificially to induce labor. She delivered within a short period but subsequently died. Autopsy showed changes in the liver and kidneys consistent with eclampsia.

FETAL MORTALITY

The mortality among the offspring of women with premature rupture of membranes was 5.4 per cent. The total fetal and neonatal mortality at the new Chicago Lying-in Hospital, since it opened in 1931, is 4.37 per cent. In the present series, as well as in the total hospital mortality, all fetuses beyond twenty-two weeks' gestation are included.

In 17.4 per cent of the cases in this series, delivery took place prior to the thirty-eighth week. Infants delivered in the same period in the total hospital series amounted to only 6.7 per cent. The mortality rate (stillbirth and neonatal deaths) for our institution shows approximately 21 times as great a mortality when delivery occurs before the thirty-eighth week as after that time. The expected mortality in the cases included in the present study would be 9.9 per cent if the same mortality rates held for term and premature infants as exist in the total deliveries. There is, therefore, actually less than the expected mortality.

The mortality rates for the previable, premature, and term infants are shown in Table VII both in percentage of deliveries and in rates per 1,000 live births. When the death rates are calculated per 1,000 live births, the total hospital previable and premature rates are considerably less than those in the group with premature rupture of the membranes, while the rate for those at term is slightly more. This is probably accounted for by the much greater proportion of mature infants among general hospital admissions.

TABLE VII. FETAL MORTALITY

PREMATURE RUPTURE MEMBRANES				HOSPITAL
FETAL AGE	DELIVERIES	DEATHS	PER CENT	PER CENT
Previable	16	15	93.7	96.61
Premature	158	25	15.8	32.66
Term	826	14	1.69	1.93
<i>Mortality Rates Per 1000 Live Births</i>				
PREMATURE RUPTURE OF MEMBRANES			HOSPITAL	
FETAL AGE	STILLBIRTHS	NEONATAL	STILLBIRTHS	NEONATAL
Previable	7.19	8.21	2.9	2.8
Premature	12.32	13.34	9.24	10.89
Term	9.24	5.13	10.89	7.07

Although the percentage mortality of the previable group should theoretically be 100 per cent, one infant survived in this group and was discharged from the hospital on the eightieth day. Subsequently it developed gliomas of the eyes and has probably since died, although this information is not available at the present time.

The reason for the seemingly high percentage of survival among the premature infants with prematurely ruptured membranes compared with the general hospital rate (15.8 per cent mortality and 32.66 per cent for the hospital) is obscure, although labor is shorter on an average than when membranes are not ruptured. Perhaps it is safe to assume that the fetal mortality rate was generally not increased by the fact that the membranes were ruptured prematurely.

The mortality percentages for the two groups vary but little at term, although here again those with premature rupture have a slightly lower death rate (1.69 per cent) than those in the general hospital group (1.93 per cent).

One of the most surprising findings in relation to mortality is that, although patients at or past forty weeks rarely fail to go rather promptly into labor following rupture of membranes, the mortality is very high among those infants who are delivered after a latent period of fifty-five hours or more (Fig. 1). Of 8 such infants four died, and all of the deaths were due to pneumonia. In association with the delivery of one there had been a prolonged first stage. Only one previable infant of the 15 examined at autopsy showed any evidence of intrauterine lung infection, although in 42.3 per cent of all the deliveries between twenty-two and twenty-nine weeks, membranes had been ruptured for over one hundred hours. Another infant from this group died of aspiration pneumonia at seventy days of age. This is in marked contrast with the infants at term where the findings are as above noted. One might theorize that previable infants do not breathe in utero, that they rarely do before forty weeks, and frequently do thereafter. See Fig. 1 for case distribution of pneumonias.

Among the 52 infants subjected to autopsy, 6 showed major malformations, 4 intracranial hemorrhages, and 2 erythroblastosis; 5 showed the petechial hemorrhages usually associated with intrauterine asphyxia. In 11 infants and fetuses, there was an inflammatory exudate in the lungs. This was associated with intracranial hemorrhage in one instance and with cardiac malformations in two instances.

Among 2,000 autopsies performed at the Chicago Lying-in Hospital on fetuses and newborn infants, pneumonia, as the only pathologic lesion, was found in 7.9 per cent of the autopsies and in an additional 3.8 per cent as a contributing cause. This is a total of 11.6 per cent which is considerably lower than the 21.2 per cent (11 in 52) found in this series.

CONCLUSIONS

1. The uterine musculature shows a progressively increasing degree of resistance to medical or mechanical induction of labor prior to term, reaching a high degree of inertia between twenty-two and thirty weeks. Vaginal or abdominal hysterotomy suggest themselves as being the safest primary termination of pregnancy at this stage.

2. There is a low maternal morbidity among patients treated conservatively with prolonged membrane rupture.

3. Because of the possibility that the patient may be in painless labor, medical induction of labor at term with membranes ruptured should be delayed ten to fifteen hours if possible.

4. There is a high fetal mortality from pneumonia among infants at forty or more weeks of gestation where the membranes have been ruptured for over fifty-five hours.

5. Based on comparative statistics, premature rupture of the membranes does not appear to be followed by an increased mortality or morbidity rate despite the increased number of operative deliveries.

DISCUSSION

DR. E. D. PLASS, IOWA CITY, IOWA.—Having already been the recipient of much unfavorable criticism because of my advocacy of premature rupture of the membranes as a means of inducing labor in indicated cases and of my extensive use of premature elective rupture on an economic and convenience basis alone, I accepted the invitation to discuss this paper with some trepidation. My acceptance was dictated largely by the desire to restate my position which has, I fear been somewhat distorted by the opponents of elective rupture. I have never, I think, taken any other position than that "The induction of labor by premature rupture of the membranes after stimulation of the uterus through the action of castor oil, quinine, and pituitary extract is safer than the other forms of mechanical irritation employed for this purpose (bougies, bags, or packing)." There has been no reason to alter this position, although it has been recognized that the procedure is not adaptable to very immature pregnancies, where some form of hysterotomy is to be preferred.

I have nowhere advocated routine elective induction of labor by this means, even though our own experience has been so satisfactory that we have continued its use even after the original experimental series were completed. Under the conditions obtaining in our own clinic with the large majority of patients coming from some distance and being supported by public funds, elective rupture becomes a social and economic question, provided only that it does not adversely affect the outcome for mother or child. By inducing labor at the calculated date when the fetus is evidently mature, it is possible to return the mother to her home a few days earlier than otherwise and thus to restore the continuity of family life, and to reduce somewhat the expenditure of state money. Other clinics and individuals must necessarily determine their attitudes according to the conditions under which they operate.

The series of cases presented by Dr. Morton largely confirms our earlier compilations and reinforces our conclusions that certain advantages apparent in labor following premature rupture of the membranes counterbalance other risks evidently connected directly with the early loss of amniotic fluid. The danger of, and practical impossibility of anticipating, a prolonged latent period argues against the method, but in both Dr. Morton's experience and in ours, this risk is not excessive and is surely justifiable at least when the induction is indicated.

The authors are evidently not enthusiastic about elective rupture, and I shall certainly not argue the point with them, but their results indicate that premature rupture of the membranes is at least not the dangerous complication which some would have it.

DR. L. W. MASON, DENVER, COLO.—After I began the practice of medicine about fifteen years ago, several incidents happened which made me wonder if what I had been taught about premature rupture of the membranes was true. At first when patients would call during the night to tell me that their membranes had ruptured, bearing in mind what I had learned that premature rupture resulted in a prolonged, inefficient, and ineffective labor, I would tell these patients to go to the hospital and I would see them the next morning. Usually the intern would call within the next three or four hours to tell me to hurry over, and frequently I did not get there in time to deliver even the placenta.

I formerly studied 1,000 cases at the University of Colorado School of Medicine, with results very similar to those reported by Dr. Morton and Dr. Plass. This material was written up and submitted in 1933 to the *Journal of the American Medical Association*. It was promptly rejected for the reason that my conclusions were contrary to current practice. These conclusions, of course, were only inescapable facts brought out by the study. About six months ago, an article was published in that Journal entitled "Changing Concepts of Dry Labor."

Previous to 1933, two papers had come to my attention, one by Schultz, of California, a study of spontaneous rupture of the membranes, and the other by Guttmacher and Douglas of Johns Hopkins, a report of the rupture of the membranes for the induction of labor. The results of all of these studies to date have been substantially the same. I found in my own series that the total average time in labor was reduced by about 60 per cent, both in primiparas and multiparas. There was no demonstrable increase in infant or maternal morbidity or mortality. Factors which prolong labor in cases in which the membranes had ruptured before complete dilatation of the cervix were found to be unrelated to the presence or absence of the intact membranes.

A factor which I think sometimes results in a long latent period after rupture of the membranes is that all the amniotic fluid is not out. In rupturing the membranes for the induction of labor one should attempt to rock the head back several times to insure that all the amniotic fluid, and not merely the forewaters, drains away. Otherwise we may have a condition that sometimes happens with slight spontaneous rupture, when the fluid may dribble away for a week or two before the onset of labor.

DR. J. W. REDDOCH, NEW ORLEANS, LA.—Since the original report of Drs. Guttmacher and Douglas we have used rather routinely artificial rupture of the membranes for induction of labor on our service at the Charity Hospital. One of our special problems is that many of our patients come in for hospitalization three or four weeks before the expected onset of labor. With this number of cases we have a fertile field for study of artificial rupture of the membranes.

The results of our studies have paralleled those of Dr. Plass. A few years ago I reviewed the first 100 cases in which there were two fetal deaths, both due to prolapse of the umbilical cord. Since then we have put the patient on her feet after rupturing the membranes and have had no more trouble with this complication. We have selected vertex cases only, in which the cervix was not thicker than three-fourths of an inch whether multipara or primipara. We have not chosen cases in which the head was above the pelvic brim.

DR. MORTON (closing).—I can assure Dr. Plass that no effort was made to have an editorial policy in this study of artificial rupture of the membranes. This series included patients who had both spontaneous and artificial rupture of the membranes.

A STUDY OF ONE HUNDRED AND FIFTEEN CASES OF RUPTURED ECTOPIC PREGNANCY*

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(From the Department of Gynecology, University of Louisville Medical School)

PROBABLY since the inception of eoneption woman has been subject to ectopic pregnancy. The first record of such a case was in 1050 A.D., but not until December, 1859, was the first surgical treatment carried out by Dr. John Bard of New York. Lawson Tait, in 1883, published the first successful series of operated cases.

We do not choose to re-state the numerous causes advanced for the production of ectopic pregnancy, but the most prominent and consistent factor appears to be the result of infection. Authorities on veterinary obstetrics say domestic animals are relatively free from infection and deformities. Dr. W. L. Williams,¹³ emeritus professor of veterinary obstetrics, Cornell University, states: "A careful search of veterinary literature fails to reveal apparently authentic cases of tubal pregnancy in domestic animals. The few actual cases of extrauterine pregnancy reported have been due to rupture of the uterus, most of which result from torsion of the uterus."

Dr. G. Fleming¹⁵ gives as his reasons for the infrequency of extrauterine pregnancies in animals:

1. Different disposition of their generative apparatus.
2. A lesser tendency of domestic animals to disease, functional disorders, and deformities.
3. Their function being only that of reproduction.
4. Ectopic pregnancy apparently is no more common in multiparas than uniparas, nor in any one species.
5. No report has been made concerning *Brucella abortus* and ectopic pregnancy.

From the above it seems that low incidence of infection, freedom from functional diseases and deformities, and exclusive use of sex organs for reproduction do play a part in the freedom from ectopic pregnancy. If this is true, we should endeavor to point out means of correction, and have more detailed studies of the cases.

At present there is no pathognomonic sign or symptom. A diagnosis rests upon a good clinical history associated with other clinical signs in an ectopic-minded physician. We are presented with ectopic pregnancy in one of three phases: (1) emergency, (2) state of deliberation, and (3) obscurity. In each of these phases our method of treatment differs.

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

We herewith present a series of 115 cases of ruptured ectopic pregnancy treated in the Gynecological Department of the Louisville City Hospital, from July 1, 1927, to January 1, 1941. Each case was confirmed by pathologic report of the specimen removed. There were 27 additional cases in which unconfirmed diagnosis of ectopic pregnancy was made, which are not included in this series.

The only constant factor in ectopic pregnancy is inconsistency.

For a more detailed study, these 115 cases have been divided clinically into three groups (Table I).

TABLE I. CLINICAL GROUPING OF 115 CASES OF RUPTURED ECTOPIC PREGNANCY

GROUP		CASES	PER CENT
I	Patients with signs of internal hemorrhage, in whom prompt operation was imperative	62	53.8
II	Patients in whom internal bleeding had stopped; surgery was instituted when patient's condition warranted	35	30.4
III	Obscure cases of long-standing, in which hemorrhage and product of conception were encapsulated	18	15.6
Total		115	99.8

Chart 1 gives the incidence of cases by years in the Louisville City Hospital. Two peaks appear which are not explained by the progressively increasing number of patients hospitalized. This gives an average incidence of 1 ectopic pregnancy in 137 deliveries in the City Hospital.

Over a period of five years in five private hospitals very little change is noted in the number of ectopic pregnancies cared for, in spite of increasing number of hospital deliveries. These hospitals admit only white patients and draw their cases from industrial and farming districts. In private hospitals the rate is one ectopic pregnancy to 78.5 deliveries (Chart 2). Note that the ratio of increase of ectopic pregnancy is greater in the City Hospital in spite of the increasing number of deliveries, while the yearly ratio remains more constant in the private hospitals in spite of increased deliveries. While most patients with ectopic pregnancies are hospitalized, a majority of abortions and deliveries are cared for in the home, and a true ratio of ectopic to normal pregnancies and abortions can scarcely be obtained. The cause for fluctuations in cases of ectopic pregnancy remains to be determined. The determination is dependent upon an accurate recording of our findings as an important cause of fetal and maternal deaths; we should insist that our vital statistics include incidence and causes of ectopic pregnancies.

Infection appears to be the dominating factor. Twenty-two per cent of our series had a definite history of previous infection before the ectopic pregnancy occurred. In the 115 cases, only 50 colored patients, and 33.3 per cent, had a positive Wassermann or history of syphilis.

One might expect a higher incidence of ectopic pregnancies in the colored race.

Cauterization of the cervix or tubal insufflation after an old pelvic inflammatory process is a rarely emphasized source of ectopic pregnancy.

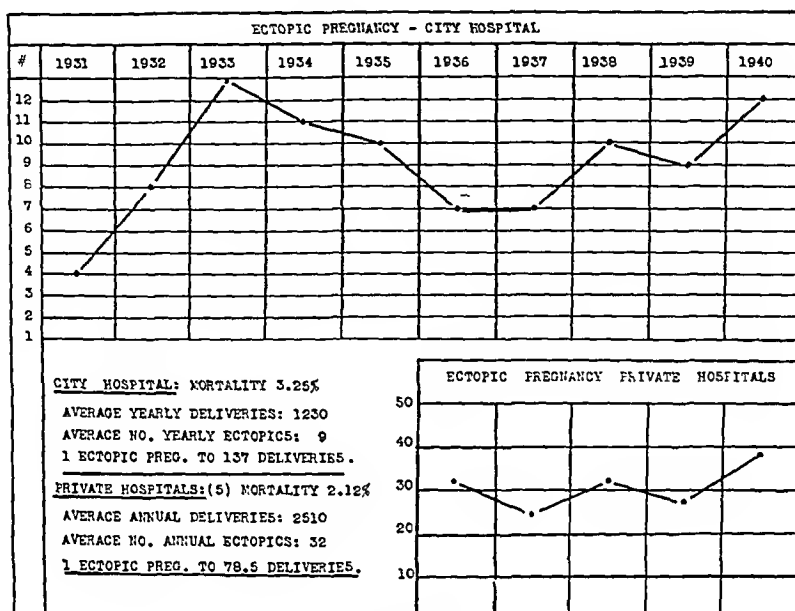


Chart 1.

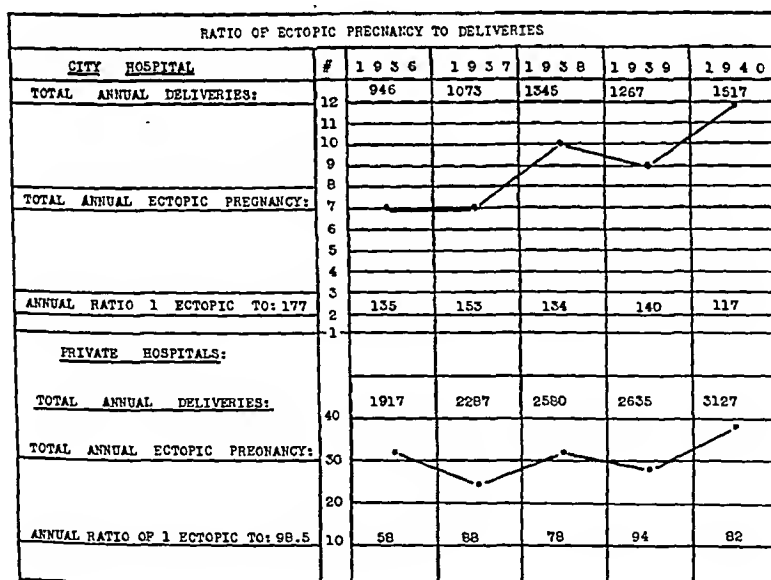


Chart 2.

In this series, 18 per cent of cases had abortions before the ectopic pregnancy; in 8.6 per cent the ectopic was the first pregnancy.

Hypoendocrine factors obviously seem to be very important causative agents, but very little evidence has been produced. Could not inade-

quately developed tubes and uteri, or inadequate circulation be as potent factors in the production of such a catastrophe as pelvic infections? Are not prolonged periods of infertility frequently the result of endocrine imbalance? May not the loss of cilia action, or absence of peristaltic motions or tubes weaken, impede, or even destroy the ingress of spermatozoa for fertilization just as readily as infection?

Endometriosis has been given as a causative factor in ectopic pregnancy. Fortunately, or unfortunately, patients with endometriosis are relatively infertile. No cases of endometriosis were noted in this series.

There were 65 white and 50 colored patients; the average age of the group was 29 years. The average age in the more acute group was six years younger than in the obscure group. Youngest case was 17 years, oldest 43.

In Group I, there were 10 cases of ectopic pregnancy as a first pregnancy. Eight patients had been married less than two years.

The age incidence by decades was as follows (Table II) :

TABLE II. AGE INCIDENCE

AGE—YEARS	CASES	PER CENT	
14-20	10	8.6	} 87%
20-30	65	57.0	
30-40	35	30.0	
40-	5	4.3	

Eighty-seven per cent of all the cases of ectopic pregnancies occurred between twenty and forty years of age. Seventy-eight per cent of all patients were multiparas with an average of 2.7 children. Five patients were married twice with pregnancies in both marriages. This points to different etiologic factors. Twenty-four patients miscarried previous to the ectopic pregnancy.

Long periods of infertility have often been listed as an etiologic factor in ectopic pregnancy. The average interval between gestations was 4.8 years (as well as could be ascertained). There were two patients with 18-year intervals; one, 16 years; three, 11 years; and three, 10 years from the previous gestation. A question of general interest would be: Were these periods of apparent infertility due to inadequate glandular function, infection, contraception, or general debility on the part of one or both partners? Can all this be explained by infections?

Over 83½ per cent of the patients had normal menstrual periods (Table III). Eleven in Group I had no period of amenorrhea. On careful study of these cases one might have found the last regular menstrual period was either abnormally short, scant, or delayed beyond the usual time. Such a history is especially important in clinching the diagnosis. The average duration of amenorrhea was less than three months in all cases; longest history was 6.5 months for an abdominal pregnancy.

TABLE III. MENSTRUAL CHANGES AND GESTATIONS

GROUP	TYPE OF MENSES	PERIOD OF AMENORRHEA	DURATION OF ABNORMAL BLEEDING	AVERAGE NO. OF PREGNANCIES AND ABORTIONS	INFERTILE
I	Regular, average duration 4 days: 47 patients Irregular, average duration 6 days: 15 patients	11, no menstrual changes Average: 1 Mo. 18 days	11 had no abnormal bleeding Average: 9 days	10 cases first pregnancy Average 2.8 pregnancies 14 abortions	Three patients: 11 yr. Three patients over 10 yr. Average: 3.2 yr.
II	Regular, average duration 4.5 days: 31 patients Irregular, average duration 5.1 days: 4 patients	Average: 2 Mo. and 4 days	7 had no abnormal bleeding Average: 20 days	Average 2.8 pregnancies 7 abortions	
III	Regular, average duration 3.5 days: 16 patients Irregular, average duration 4 days: 2 patients	Average: 2 Mo. and 13 days	5 had no abnormal bleeding Average: 17 days	Average 2.4 pregnancies 6 abortions	Two patients: 18 yr. Average: 4.8 yr.

Pain, of which there are at least five different types, was present in our cases, 91 per cent giving pain as their chief complaint, and most constant symptom. Fifty per cent of the pain was cramp-like in character (Table IV).

In Group I, the pain was more often sharp and stabbing. When this type of pain, radiating to the rectum (so-called "bath-room sign") was associated with collapse, it was of the greatest significance. Rigidity of abdomen was unusual in these cases, in contrast to the abdomen of infection.

Vaginal bleeding occurred in 60 per cent of cases as the chief complaint in the acute group, and in 50 per cent of the obscure cases. Nausea, vomiting, dysuria, and urinary frequency occurred in over 50 per cent of the acute cases, to lesser degree in the more obscure cases where the peritoneal irritation had begun to subside.

The pelvic finding, in about 50 per cent of the cases, was a mass in the posterior cul-de-sac. In the majority of instances the mass in the side was fairly frequently associated with the side in which the pain was greater, and as frequently located in right as in left side.

Comparison of the three groups shows greatest increase in symptoms of Group I over Group III, especially in abdominal tenderness and distention, with 32.5 per cent of cases showing shifting dullness in acute cases.

The laboratory findings (Table V) show a definite anemia in all groups, with leucocytosis in Groups I and II, but not much variation in differential count. Urine examinations, in the majority of instances, were normal.

TABLE IV. CLINICAL FINDINGS

GROUP	CHIEF COMPLAINT	SYMPTOMS	PELVIC FINDINGS
I	Abdominal pain: R. L. Q. 25—40.3% L. L. Q. 17—27.4% Both L. Q. 20—32.2% Vaginal bleeding 37—60.0% Abdominal tumor 2—3.0%	Vaginal bleeding 38—60.8% Leucorrhea 32—51.7% Vomiting 38—60.8% Nausea 15—24.2% Dysuria, frequency 12—19.5% Weakness 13—20.0% Fainting 11—18.7% Shoulder pains 9—15.0% Dyspnea 6—10.0%	Pelvic mass: R. L. Q. 20—32.2% L. L. Q. 15—24.1% Posterior 27—43.5% Soft cervix 35—56.8% General abdominal tenderness 56—91.0% Abdominal distention 47—77.2% Shifting dullness 20—32.5% Shock 12—19.3% Enlarged uterus 27—43.0%
62			
II	Abdominal pain: R. L. Q. 12—34.2% L. L. Q. 10—28.5% Both L. Q. 13—37.1% Vaginal bleeding 23—66.0% Abdominal tumor 2—5.7%	Vaginal bleeding 21—60.2% Leucorrhea 20—56.0% Nausea 22—62.4% Vomiting 19—54.1% Dysuria, frequency 11—30.0% Breast changes 7—20.3% Weakness 24—73.0%	Pelvic mass: R. L. Q. 9—25.7% L. L. Q. 11—31.4% Posterior 15—43.8% Soft cervix 14—41.0% General abdominal tenderness 23—67.0% Abdominal distention 13—36.0% Enlarged uterus 26—74.5% Bloody vaginal discharge 15—41.6%
35			
III	Abdominal pain: R. L. Q. 7—38.8% L. L. Q. 3—16.6% Both L. Q. 8—44.4% Vaginal bleeding 9—50.0% Abdominal tumor 2—11.1%	Vaginal bleeding 10—58.0% Leucorrhea 9—50.0% Nausea 5—25.0% Vomiting 6—33.0% Frequency 3—16.6% Weakness 2—10.0%	Pelvic mass: R. L. Q. 5—27.7% L. L. Q. 3—16.6% Posterior 10—55.5% Soft cervix 10—55.5% Enlarged uterus 9—50.0% General abdominal tenderness 10—55.5% Abdominal pregnancy 2—11.1%
18			

The most informative study is that of admission temperature, blood pressure, and pulse rate. In Group I, there was found an average rise of more than 25 points in pulse rate, with a fall of more than 27 points in systolic blood pressure. Thirty-six per cent of Group I had subnormal temperature or were in shock upon admission.

Our attitude toward laboratory procedures, used as diagnostic aids in this group, is that while the Aschheim-Zondek or Friedman tests may be confirmatory of a pregnancy, they are not a constant aid for they remain positive only as long as the fetal cells secrete hormone into the maternal blood, and twelve hours is the shortest period of time in which an accurate reading can be obtained. Many of the patients with severe cases would have died unless immediate treatment had been instituted. Falls-Freda and Cohen colostrum pregnancy test may develop to be of

TABLE V-A. LABORATORY FINDINGS

GROUP	R. B. C.	W. B. C.	HEMOGLOBIN	P. M. N.	SEDIMENTA- TION
I	Average 2,937,000	Average 10,654	Average 8.4 Gm. (Sahli)	Average 78%	27 Cases (68% Negative)
II	Average 3,523,119	Average 9,803	Average 10.5 Gm. (Sahli)	Average 73%	18
III	Average 3,966,080	Average 6,825	Average 10.9 Gm. (Sahli)	Average 72%	15

TABLE V-B. LABORATORY FINDINGS

GROUP	WASSERMANN	ASCHHEIM- ZONDEK	BLOOD PRESSURE	PULSE	P. O. TEMP. RISE
I 62	18% of all white cases were positive	15 2 Positive	91/60	100	101.4° F. Normal in 4.5 days
II 35		11 (All negative)	110/72	98	100.2° F. Normal in 4.5 days
III 18	33% of all colored cases were positive	6 (All negative)	118/75	90	100.4° F. Normal in 6 days

great benefit in excluding abdominal infection and other interperitoneal hemorrhages. In doubtful cases, a positive Aschheim-Zondek test strongly suggests the presence of pregnancy; negative, not always true. In face of a positive Aschheim-Zondek one must be cautious.

A positive, delayed, direct van den Bergh reaction is of help in that it indicates the presence of free blood in the abdominal cavity.

Diagnostic posterior colpotomy with aspiration of fluid may be of help; it was helpful in 6 cases of our series.

Sedimentation tests were run in one-third of the cases, and were sixty minutes or over, which is well within normal range. Only 8 per cent of these cases having sedimentation tests were abnormal, and these were associated with pelvic infections. Sedimentation test is not of importance in differentiating inflammation from ectopic pregnancies.

Hysterosalpingography is an adjunct in the more obscure cases, where patient is not too ill for the procedure and infection not present; and is excellent in differentiation of rupture of follicle cyst with bleeding and ectopic pregnancy.

We wish to emphasize some of the rather frequent clinical findings, which are not usually emphasized in this type of case:

1. Softening of the cervix occurs in over 50 per cent of the cases, and exquisite sensitivity of the cervix to motion is a very important finding. This is due to changes associated with pregnancy and the

peritoneal irritation from the blood gravitating from the ends of the tubes, or ruptured tubal walls, into the cul-de-sac, affecting the uterosacral ligaments, resulting in pain on motion.

2. Enlargement of the uterus, general abdominal tenderness and distention without rigidity, with unilateral mass in 50 per cent of cases.

3. Low or subnormal temperature and progressive anemia with leucocytosis.

4. Unilateral pulsation of the uterine artery frequently found. The uterus is usually displaced downward and making it more accessible to the examining finger, with sudden, excessive demand for blood supply increases the activity of the artery on the affected side.

For a woman of childbearing age, the association of a previously abnormal period, or period of amenorrhea with abdominal pain or abnormal bleeding should always bring to mind the possibility of ectopic pregnancy. *Remain ectopic-minded.*

Ectopic pregnancy warrants operation when diagnosis is made. There is no conservative treatment for ectopic pregnancy. In my opinion, it is better to make the mistake of opening an abdomen of questionably early pelvic inflammatory disease than to have a death from hemorrhage with ectopic pregnancy.

TABLE VI

GROUP	SURGERY		PATHOLOGY		RESULTS
I	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, pneumonia four days post-operative
62	Right	21—33.9%	Salpingitis, chronic	8—13.0%	
	Left	25—40.3%	Ovarian cyst	2—3.2%	
	Bilateral	6—9.6%			
	Oophorectomy	4—6.4%			
	Appendectomy	5—8.0%			
	Transfusion	21—33.9%			
	Autohemotransfusion	17—27.4%			
II	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, concealed hemorrhage 1 Dead, peritonitis
35	Right	21—60.0%	Salpingitis, chronic	6—17.1%	
	Left	7—20.0%	Oophoritis	1—2.8%	
	Bilateral	7—20.0%	Uterine fibroids	2—5.7%	
	Oophorectomy	3—8.5%	Abdominal pregnancy	3—8.5%	
	Appendectomy	15—42.8%			
	Fundic Hysterectomy	4—11.4%			
	Autohemotransfusion	7—20.0%			
III	Salpingectomy		Ectopic pregnancy	100.0%	1 Dead, shock and hemorrhage postoperative Mortality 3.05%
18	Right	3—16.6%	Salpingitis, chronic	6—33.3%	
	Left	2—11.1%	Oophoritis	2—11.1%	
	Bilateral	13—72.2%	Abdominal pregnancy	2—11.1%	
	Oophorectomy	5—27.7%			
	Appendectomy	14—77.7%			
	Hysterectomy	9—50.0%			
	Transfusion	6—33.3%			

The types of surgery are quite different in the three groups (Table VI). In the acute group, a greater number of autohemotransfusions and transfusions are carried out, 40 per cent being transfused either before or during the operation.

Seventy-three per cent of acute cases had unilateral salpingectomy without hysterectomy. This is done only as a life-saving measure. We

do not advocate converting acute cases into chronic cases so that more deliberation can be carried out, but recommend the minimum curative surgery.

In Group II there were 80 per cent unilateral salpingectomies with 11 per cent hysterectomies, and fewer transfusions. In this group the patient could be better prepared for operation.

Group III had 27 per cent unilateral salpingectomies and 50 per cent hysterectomies. This was a correction of the pathology at hand for permanency of results in patients properly prepared.

Such an attitude necessitates the separation of ectopic pregnancy into groups, and reveals why different types of surgery are done in ectopic pregnancy.

The average time of operation in Group I was fifty-five minutes, the shortest twenty-five minutes; in Group II, eighty-eight minutes; and in Group III, ninety-five minutes. Time is indeed a factor in the handling of these severely shocked patients, and it is important to reckon with it.

Anesthesia is also important. In our cases either local, or carefully administered cyclopropane anesthesia was given.

Patient's hospitalization averaged 18.5 days; 30 per cent of the patients remained in the hospital over twenty-one days.

Correct diagnosis preoperatively was made in 71 per cent of cases in Group I, 48 per cent of cases in Group II, and 16 per cent of cases in Group III.

In this series there were five abdominal pregnancies, the result of tubal abortions. The oldest was apparently a six months' gestation. In all of these the products of conception were nonviable before operation was performed.

There were four deaths: one in Group I from pneumonia, two in Group II from concealed hemorrhage and peritonitis, and one in Group III from shock and hemorrhage, giving a mortality rate of 3.05 per cent.

In postoperative follow-up an average of two visits in three months show 13.3 per cent had increase in vaginal discharge, with 5 per cent having increase in menstrual pain. In all cases where the uterus was not removed, menstrual function had returned.

Prompt, conservative surgery, transfusions, and postoperative supportive treatment will miraculously transform a desperate case to one with a relatively smooth convalescence in a short period of time.

SUMMARY

1. Presentation of 115 cases of ruptured ectopic pregnancy, giving the incidence and comparison with private hospitals, and the ratio of ectopic pregnancies to births in the city and private hospitals.

2. Division of cases into three groups (I. acute emergencies, II. deliberate surgery, III. obscure cases) with comparison of the clinical findings, as to age, race, clinical symptoms, physical and laboratory

findings, showing that there is a difference in the three groups, and a necessity for differentiation in the type of treatment.

3. Emphasizing that careful history and summary of clinical findings, varied types of pain, subnormal temperature, abdominal distention without rigidity, soft cervix, enlarged uterus, and leucocytosis in a woman of the childbearing age should keep one "ectopie-minded."

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DISCUSSION

DR. HILLIARD E. MILLER, NEW ORLEANS, LA.—Dr. Johnson's study of 115 cases of ectopic pregnancy from a public institution in Louisville suggests some interesting comparisons with a similar study of 137 cases which I made last year from Touro Infirmary, a private institution in New Orleans. The age range in both series was the same, 17 to 43 years, and in both the highest incidence occurred in the period between 20 and 40 years. In both series the mortality was unusually low, 3.05 per cent in Dr. Johnson's series from the public hospital, and 2.18 per cent in my own from a private institution, where, as would naturally be expected, patients are seen earlier and in better condition.

In both series the great majority of patients complained of pain, which was of several different kinds. Pain is, however, a symptom common to a great many diseases and far more valuable from the standpoint of diagnosis is the history of any sort of menstrual irregularity. Frank amenorrhea was present in more than half the cases in my series, and in one-sixth of the patients in Dr. Johnson's series. Four-fifths of the patients in my series, however, presented a history of irregular bleeding, irregular in relation to the normal time of the period and atypical in relation to the type of bleeding. The abnormally dark color of the discharge is characteristic. When the history is being taken in a case in which one suspects ectopic pregnancy, the questioning should be detailed on these various points. A simple inquiry as to whether a period has been skipped is not sufficient, and the usual patient will not supply the additional details unless she is specifically asked about them.

From the standpoint of physical findings, tenderness, which is present in most cases, and rigidity, which is present in a fair number, are no more useful *per se* from the standpoint of diagnosis than is pain. On the other hand, the finding of a mass either by abdominal or by pelvic examination is important, and sensitivity of the cervix on motion is present in perhaps half of all cases; I am inclined to regard this finding as almost pathognomonic, though its absence, of course, is not significant.

Though aware that a physician who uses the words "always" and "never" is looking for trouble, I nonetheless am willing to make the unqualified statement that the treatment of ectopic pregnancy is surgical, and that surgery should be performed as soon as the diagnosis is made. I am not in favor of delaying operation for any reason at all. It is quite true that in many instances delay does no harm, but there is no way of determining the cases in which it will do no harm as distinguished from those in which it will do a great deal. Even though the patient is in shock, operation should still be carried out without delay. The shock is due to hemorrhage, and its logical treatment is the control of hemorrhage. Opening the abdomen and tying off the bleeding vessel or removing the tube, if carried out gently and rapidly, under light anesthesia, does not add to the shock. Adjuvant measures, such as infusion, or preferably, transfusion, can be carried out equally easily and far more profitably in the operating room, while the fundamental trouble is being corrected.

The clear-cut case of ectopic pregnancy is so obvious that the diagnosis can scarcely be missed. The obscure case can furnish as difficult a problem as any phase of gynecology. If the confusion is with another condition for which immediate surgery would be demanded, as for instance appendicitis, there is really no problem, for one merely operates at once, with the acute condition in the abdomen as the general background. If the confusion is with a condition for which emergency surgery is unnecessary or is actually undesirable, the problem is less simple, though my own opinion is still that if the mere suspicion of ectopic pregnancy exists, no time should be wasted on refinements of diagnosis. Less harm is done by opening the abdomen in pelvic inflammatory disease than by withholding it in possible ectopic pregnancy. Furthermore, if definite diagnosis is impossible, I should personally prefer exploratory laparotomy to either of the diagnostic methods suggested by Dr. Johnson. I have no doubt that colpotomy and hysterosalpingography both yield useful information, but I question whether it is worth the additional risk both methods seem to introduce.

I also take issue with Dr. Johnson as to the performance of any type of hysterectomy in ectopic pregnancy, except on indications for which the uterus would be removed under any circumstances, and with the further provision that the patient's condition warrants the additional surgery. The object of hysterectomy, as Dr. Johnson states, is to insure permanent results, in other words to guard against recurrence. In my own series of 137 cases there were 5 recurrences, 3.6 per cent, which, curiously, is exactly the incidence of recurrence reported by Smith in a collected series of 1,608 cases of ectopic pregnancy.

I grant the risk, actual and potential, of ectopic pregnancy, but I still question whether a risk of recurrence of less than 4 per cent justifies the sterilization of a woman in the child-bearing years, particularly if she has no other living children. If Dr. Johnson has the figures available, I hope he will mention the percentage of recurrence in his series. I should also like to know the age and race of the women submitted to this radical procedure, both of which, of course, may throw a very different light upon the matter.

DR. WILLIAM D. PHILLIPS, NEW ORLEANS, LA.—A rather unique experience of a few days ago brought out one point which I have not heard mentioned, namely the extreme leucocytosis in acute rupture of an extrauterine pregnancy. I would like to ask Dr. Johnson whether he has had a similar experience.

The patient on whom I made this observation presented no symptoms of pregnancy. Her only symptom was a slight upper abdominal discomfort which I regarded as due to some gastric disturbance. While in the radiologic laboratory, this patient suddenly collapsed and was sent to the hospital where her blood pressure was 58 systolic and 39 diastolic. The blood count showed 4,000,000 red cells, 69 per cent

hemoglobin and 48,000 leucocytes. A second count later showed 2,925,000 red cells, 35 per cent hemoglobin and 35,000 leucocytes. A third count showed much the same figures. Vaginal examination disclosed only a slight tenderness on pressure on the right side, and as the cervix was moved upward there was pain. Dr. Musser, Professor of Medicine at Tulane University, expressed the opinion that she had a hemorrhage and stated that acute hemorrhage in the abdominal cavity would give a high leucocyte count. We operated upon her and found an opening about the size of my right thumb into the horn of the right tube. She is now doing quite well.

DR. DAVID A. HORNER, CHICAGO, ILL.—An important point to consider is, when does an ectopic pregnancy become an abdominal pregnancy. Occasionally there are good reasons for not operating at once, especially if it has been some time between the apparent rupture and admission to the hospital. I have at the present time two ectopic pregnancy babies going to school, simply because the mothers were not operated upon at the time the rupture of the pregnancy occurred.

Chronic ectopic pregnancy (I think I can call it that) is seen more often in charity hospitals than in private practice. The chronic case is the acute one which was unoperated upon and which went on to recovery, the acute symptoms subsiding when the extruded mass developed to term or was totally absorbed.

The point I wish to bring out is that it is not necessary to operate upon all ectopics immediately on diagnosis. Stilbestrol will stop functional uterine bleeding but will not stop a case of uterine bleeding following a ruptured ectopic pregnancy. Hence this point may help in the diagnosis of some cases of ruptured ectopic pregnancy.

DR. KARL JOHN KARNAKY, HOUSTON, TEXAS.—I am at the present time studying the cases of ectopic pregnancy at the Jefferson Davis Hospital, Houston, Texas. In the cases from 1932 to 1933, which have so far been reviewed, there were 11 white women, 5 Mexicans, and 16 colored women, a total of 32 cases. The ages were from 17 to 49, the majority of cases were at the age of 24 years.

The preoperative diagnoses were as follows: ectopic, 11; infected abortion, 2; acute salpingitis, 3; pelvic tumors, 2; tuboovarian abscess, 5; and acute abdomen, 3.

One point of interest was brought out by 6 cases of ectopic pregnancy referred to the Menstrual Disorder Clinic of the Jefferson Davis Hospital because of vaginal bleeding. When we gave these women stilbestrol to control their uterine bleeding, they did not stop bleeding.

DR. E. F. SCHNEIDERS, MADISON, WIS.—There are two procedures that have been of great value in the treatment of patients in extremis after trips to the hospital from rather distant points. One is the use of autotransfusion. I have resorted to autotransfusions in a number of practically moribund patients with success. In many of these cases we have dipped the blood by means of a sterile glass into a beaker, filtered it through triple gauze into citrate solution and have then transfused these patients with their own blood.

The other point was the use of large transfusions. Some patients have been in so much shock and have lost so much blood that the ordinary amounts are not adequate. In such patients we have used up to 1,500 or 1,800 c.c. of blood. We have cross-matched donor to donor to avoid possible allergic reactions and have tried not to use donors who have had a recent meal. The blood banks and the use of plasma may obviate the necessity of either autotransfusions or massive transfusions, but in the past these two measures have been of distinct help in our practice, and I believe are worthy of use when immediate donor or blood bank is not available.

DR. E. W. FISCHMANN, CHICAGO, ILL.—I wish to defend the exploratory colpotomy in preference to diagnostic cul-de-sac puncture. In a great many cases by exploratory colpotomy we have been able to inspect both tubes and in some have been able to remove the tube containing the ectopic pregnancy. Often this can be done very nicely under local anesthesia. In some cases, on the other hand, we have found it easier to cut the vesicouterine pouch than the rectouterine pouch. We firmly believe that the vaginal route is one that should be practiced more often than the abdominal route, particularly where the diagnosis is not certain.

Another point I might emphasize in the operative treatment of ectopic pregnancy is that the simultaneous removal of the appendix in these cases adds to the hazard of the operation. We have found in a study of our cases at the Cook County Hospital that simultaneous removal of the appendix in cases of ectopic pregnancy definitely increases the morbidity and mortality in these cases.

DR. JOHNSON (closing).—We have classified our cases into three groups, as they were admitted to the hospital, and attempted to show that although they are all ruptured ectopic pregnancies, they require three different types of surgery. The majority of the operative work was done by the resident staff. We do not advocate removal of appendices in any case with blood in the peritoneal cavity.

In the more acute group, 60 per cent of cases had transfusions, with only unilateral salpingectomies being performed. In the second group, only 31 per cent had transfusions, with indicated surgery carried out. The patients in the third group were admitted, in most instances, as cases of pelvic inflammatory disease. Only 16 per cent of these had a correct diagnosis before operation, yet they were ruptured ectopic pregnancies from two to six months after the rupture. In these cases we advocate correction of the pathology presented.

We emphatically believe in immediate operation on the acute cases of ectopic pregnancy, and the more radical work was carried out only in cases of long standing, and in those patients over 35 years of age. We do not advocate radical surgery on young women.

In reference to Dr. Phillip's case, we had a few cases with leucocytosis of from 25,000 to 30,000 white blood cells. I do not present this as a diagnostic point, but the cases with the highest counts were usually those with cornual ruptures, or massive hemorrhage. In those cases we see the most profound shock.

Dr. Horner advocates conservatism on abdominal pregnancies. All of the fetuses in the abdominal pregnancies in our series were dead at time of operation, and we considered these as tubal abortions. We do not, however, practice conservatism with ruptured ectopic pregnancies or abdominal pregnancies, for the maternal mortality will be higher, and, considering the deformities associated with abdominal pregnancies, we prefer to save the mother rather than have a deformed child.

Dr. Fischmann's exploratory colpotomy in skilled hands may be satisfactory, but I do not care to have my hands tied by removing a ruptured ectopic pregnancy per vaginam, and then have an ascending infection follow. The first principle of good surgery is to have proper exposure. Vaginal exploratory colpotomy does not lend itself readily to adequate exposure with ectopic pregnancy. Diagnostic puncture of posterior cul-de-sac is of diagnostic importance.

Dr. Schneiders is right in advocating large transfusions. We gave transfusions in 60 per cent of the first group, and anywhere from 1,500 to 2,000 c.c. of blood or plasma were used. Massive transfusions are excellent when indicated, and we should never overlook the use of the patient's own blood when found in the peritoneal cavity.

CLINICAL APPLICATION OF ERGONOVINE DURING THE THIRD STAGE OF LABOR*

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ERGOT was first introduced into obstetric practice by Stearns as "pulvis parturiens," but a few years' experience with administration during labor, according to his recommendation, proved that it was too powerful and dangerous for that purpose. It soon became an established conviction that this drug should not be exhibited until the uterus was empty, and today it is commonly considered that oxytocic drugs, especially ergot, cannot safely be given until after expulsion of the placenta.

Isolation of the water-soluble, oxytocic principle, ergonovine, has provided the profession with a dependable ergot preparation suitable for intravenous use, and has stimulated search for further clinical applications. More recently, certain clinics have reported that ergonovine given intravenously just before completion of the second stage hastens separation of the placenta, reduces the average blood loss, and diminishes the incidence of post-partum hemorrhage. The procedure is, however, still controversial.

Prior to April 1, 1940, oxytocics had rarely been given at the University of Iowa until after expulsion of the placenta. The exceptions included the occasional instances of third-stage hemorrhage from incomplete placental detachment or unusual prolongation of this stage of labor. No attempt was made to deliver the placenta until there were evidences of separation or the appearances of unusual bleeding. Beginning April 1, 1940, ergotrate (grain $\frac{1}{320}$) in solution was routinely injected intravenously into an antecubital vein with delivery of the anterior shoulder in vertex presentations and at the time of extraction of the head in breech. At the first ensuing contraction, the uterine fundus was grasped by the Credé grip and strong pressure was exerted to expel the placenta, which was usually born within three minutes of the birth of the child.

This study concerns the evidence obtained in 1,960 consecutive deliveries between April 1, 1940, and March 31, 1941, when intravenous ergonovine was used routinely in the great majority of patients, as compared with the results in the preceding twelve-month period, when oxytocics were ordinarily not given until after expulsion of the placenta.

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

The material in the two series was reasonably similar. Sixty-five per cent of the women in each series were parous. Ante-partum bleeding due to placenta previa or abruptio placentae occurred in nine of the ergonovine group and in five of the controls. The birth weights were comparable, as was the incidence of multiple pregnancy and other factors predisposing to uterine atony.

PROCEDURE

Post-partum hemorrhage has been defined, in accordance with common practice, as the loss of 600 or more cubic centimeters of blood.

A sterile basin held against the perineum during the period of active bleeding was employed for collection of blood. Additional and uncollected blood was "estimated" and added to make the total loss. It is recognized that values obtained in this fashion are subject to criticism, but it is believed that the method at least indicated abnormal blood loss with reasonable accuracy. For the purpose of this study, and in view of the method of collection, patients who lost between 500 and 600 c.c. of blood are included.

RESULTS

Incidence of Hemorrhage.—The actual incidence of bleeding in excess of 500 c.c. is shown in Table I. It is evident that the loss of more than

TABLE I. INCIDENCE OF POST-PARTUM HEMORRHAGE

YEAR	TOTAL DELIVERIES	PATIENT WITH POSTPARTUM HEMORRHAGE		REMARKS
		NUMBER	PER CENT	
Pre-ergonovine group; 4-1-39 to 3-31-40	1761	181	10.3	Oxytocic usually not given until after delivery of the placenta
Ergonovine group; 4-1-40 to 3-31-41	1960	78	4.0	Ergonovine given before delivery of the placenta

500 c.c. of blood was diminished considerably by the injection of ergonovine early in the third stage.

Figures for the two series were then grouped according to the total blood loss (Table II). It is now evident that the use of ergonovine

TABLE II. THE INCIDENCE OF POST-PARTUM HEMORRHAGE AT VARIOUS LEVELS

BLOOD LOSS IN CUBIC CENTIMETERS	CONTROL SERIES (1,761)		ERGONOVINE SERIES (1,960)	
	NO.	%	NO.	%
500- 600 (minimal hemorrhage)	100	5.6	37	1.8
601- 800	42	2.5	18	0.9
801-1,000 (excessive hemorrhage)	17	1.0	11	0.56
1,001-1,499	19	1.1	9	0.45
1,500 and over	3	0.17	3	0.15
Total (over 600)	81	4.6	41	2.1
Total (over 500)	181	10.3	78	4.0

reduced the blood loss in the 500 to 600 c.c. group, as well as in the cases of post-partum hemorrhage as defined earlier. Blood losses of more than 600 c.c. occurred in 81 (4.6 per cent) of the 1,761 control cases, as against 41 (2.1 per cent) of the 1,960 given intravenous ergonovine. Except in the small groups which suffered excessive blood losses (over 1500 c.c.), the ratio between the two series approximated 2:1.

"Retained placenta" was diagnosed when the third stage was protracted two hours or longer, while "partially detached placenta" included those cases in which unusual bleeding before delivery of the organ demanded intervention. By these definitions there were 4 retained placentas, 3 in the ergonovine and 1 in the control series. The blood loss ranged from 700 to 1,450 c.c. Manual removal of the placenta was performed three times (2 ergonovine and 1 control) after liquid distention of the umbilical cord and placenta and Credé maneuver under anesthesia had proved unsuccessful. In the fourth instance, Credé expression was successful.

Partially detached placentas were encountered in 10 patients (6 ergonovine and 4 control). The blood loss varied from 800 to 2,000 c.c. In 2 of the control series, distention of the cord and placenta made Credé expression of the organ possible, while in the remaining 8, manual removal was necessary.

In 2 undiagnosed twin pregnancies, ergonovine was given just before birth of the first child, but delivery of the second fetus offered no complication. In cases of multiple pregnancy generally, the loss of more than 500 c.c. of blood was reduced from 1:3 to 1:17 by the injection of ergonovine.

On the other hand, there was no appreciable reduction in the incidence of high blood loss in women giving birth to children weighing more than 4,000 Gm. In both groups, approximately 10 per cent of these mothers lost more than 500 c.c. of blood.

Operative delivery generally increased the blood loss and the indicated use of ergonovine did not effect this cause of post-partum hemorrhage. In the control year, 20 per cent of the hemorrhages occurred in operative cases, while in the following twelve months the incidence was 28 per cent. During the two one-year periods, the operative incidence was between 12 and 15 per cent. In at least one-third of the hemorrhages associated with operative intervention, cervical or perineal lacerations explain the excessive blood loss, whereas in the remainder, uterine atony, possibly incident to deeper and more prolonged anesthesia appeared to be of etiologic significance.

Excessive bleeding attributed to uterine atony occurred only once in 217 cases (0.46 per cent) among the ergonovine series, as against one in 55 (1.8 per cent) among the controls. As usual, over-distention of the uterus by twins, hydramnios, and large babies predisposed to inertia.

Prolongation of labor (thirty hours or more) produced no appreciable effect, whereas precipitate labors (less than three hours) predisposed to excessive bleeding. The use of ergonovine seemed to reduce bleeding from this cause, since there were less than one-half as many blood losses of 500 or more cubic centimeters in the ergonovine than in the control group. Presumably the oxytocic acts by preventing the lag of uterine contractions after its tumultuous first- and second-stage activity.

The intrapartum use of posterior pituitary extract is said to increase the incidence of post-partum hemorrhage (Reich, 1939). This oxytocic was not employed during labor in either series here reported, but was administered to approximately one-half the individuals in both groups as a part of the induction of labor. There was no evidence that such use influenced the post-partum blood loss.

Puerperal Morbidity.—The diagnosis of febrile puerperium is made whenever the temperature rises to 100.4° F. or more on any of the first ten days after delivery. Temperatures are recorded six times daily at four-hour intervals. Among the patients of the ergonovine series such febrile reactions occurred in 34.8 per cent, while in the control group the incidence was 38.6 per cent. This difference (3.8 per cent) is not significant, particularly since more attention was given to the replacement of lost blood during the year when ergonovine was employed as a routine.

Maternal Deaths.—There were 3 maternal deaths associated with excessive bleeding in the series treated with ergonovine, but none among the controls (Table III). Each death was associated with unusual blood loss, but, except in one instance, there was no reasonable basis for implicating the administration of ergonovine. One patient had placenta previa with post-partum uterine atony and died from shock; another had eclampsia and developed severe shock with hemorrhage after delivery. In both instances, transfusions were ineffective although given promptly from the blood bank. The third death followed a poorly managed premature and prolonged labor. The placenta did not detach completely and was retained behind a constriction ring, together with a considerable quantity of clotted blood. Attempts to complete separation by inflation of the placenta and by the Credé maneuver were unsuccessful, and manual removal was done four hours after birth of the baby. In spite of intravenous fluids, blood transfusions, and other usual antishock measures, death occurred an hour later.

DISCUSSION

The ultimate fate of any new clinical procedure depends upon two factors: it must not lead to any harmful reactions, and it must be better than its therapeutic predecessor. All treatments are eventually judged by such standards. When a procedure is designed to replace

TABLE III. MATERNAL DEATHS

CASE	PARITY	AGE	PRESENTATION	TRANSFUSION IN C.C.	DURATION OF LABOR	DURATION OF THIRD STAGE	METHOD OF DELIVERY	BLOOD LOSS IN C.C.	WEIGHT OF BABY IN GRAMS	REMARKS
40-10112	vi	29	R.O.A.	1500	2 hr., 42 min.	2 min.	Version and extraction	2,000	3,850 (still-born)	Placenta previa; postpartum uterine atony; no anesthesia. Died 10 minutes after delivery.
41-1867	0	20	R.S.A.	350	10 hr., 23 min.	9 min.	Breech extraction	750	2,800 (still-born)	Eclampsia; shock; uterine atony post partum; no anesthesia; died 13 hours after delivery.
41-1559	iii	25	R.O.A.	500	30 hr., 38 min.	4 hr.	Spontaneous	1,300	2,230 (alive)	Hypertensive cardiovascular disease; Partially detached placenta; shock; nitrous oxide anesthesia; died one hour after delivery.

therapy which has behind it a long and honored tradition, it must be viewed very critically.

There is good evidence to indicate that during the normal third stage placental detachment occurs with the first uterine contraction. Expulsion of the afterbirth into the lower segment or vagina is a function of succeeding contractions, and spontaneous expulsion from the vagina may take some hours. Because of the slowness of this last part of the phenomenon, it has long been considered good practice to expel the placenta by uterine pressure as soon as there are signs that it has been extruded from the uterine cavity.

The present experimental procedure is designed to hasten the earlier phases of the mechanism of placental expulsion by increasing the strength and amplitude of the initial third-contraction which detaches the organ. Prompt expulsion is then prompted by uterine pressure.

The mere fact that the new technique materially shortens the third stage should not be given serious consideration, since speed at this time is of no consequence. If, however, it can be shown that the blood loss is reduced, the number of post-partum hemorrhages diminished, and that serious complications of the third stage are not increased, then the procedure must receive serious consideration. Except in institutions with plenty of personnel, the plan will not prove practicable, because it demands an additional assistant to give the injection at exactly the proper time and to follow through with properly directed uterine pressure.

The data presented indicate that, when properly carried out, the intravenous injection of a therapeutic dose of ergonovine just preceding expulsion of the shoulders (in vertex presentations) or of the after-coming head (in breech presentations) is practically devoid of serious consequences and is effective in reducing the incidence of post-partum hemorrhage due to uterine atony. This experience confirms that of other observers (Reich, 1939; Eastman, 1939; Davis, 1940). It was, however, noted that more than 50 per cent of post-partum hemorrhages occurred within five minutes of expulsion of the child as against 15 per cent in the control group. This change may be attributed to the early vigorous uterine pressure required by the technique. The evident increase in the number of retained placentas (3 as against 1 in the controls) with the greater number of hemorrhages from partial separation of the placenta in the same group (6 to 4) makes the combined incidence of these more serious anomalies of placental separation and expulsion, 9 in the group receiving ergonovine and 5 in the control group. It appears that this type of intervention increases these major difficulties. This would, of course, constitute a very valid argument against the new practice, since a large part of the third-stage hazard revolves around these complications. It should, however, be recognized that this use of

ergonovine requires accurate timing to attain its maximal value and that experience is necessary to ascertain the proper time for the injections.

Sufficient time has not yet elapsed and accumulated experience is not yet large enough to permit accurate evaluation of the procedure. Consequently, it seems reasonable for the clinics interested to continue their experiments until the combined data become statistically significant. At present it is probably preferable that institutions with a minimal number of birth-room assistants refrain from employing this type of interference with the normal mechanism of the third stage. By and large, attempts to improve upon nature are not eminently successful.

CONCLUSIONS

The intravenous injection of ergonovine shortly before the conclusion of the second stage of labor appears (1) to shorten the placental stage, (2) to diminish the average blood loss, (3) to reduce by one-half the number of patients who suffer post-partum hemorrhages, but (4) to almost double the incidence of the more serious anomalies of the third stage, retained placenta and partially detached placenta.

This technique should still be viewed as experimental and should not be adopted generally until sufficient evidence has been accumulated to permit a reliable statistical evaluation of its associated dangers.

Ergot is manufactured as "ergotrate" by Eli Lilly and Company.

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DISCUSSION

DR. HARRY A. PEARSE, DETROIT, MICH.—Dr. Diddle has used 500 to 600 c.c. of blood loss as his criterion for diagnosing post-partum hemorrhage. Since women vary considerably as to how much blood loss they will tolerate, Pastore and others state that it should be expressed in terms of body weight, 1 per cent or more loss being indicative of post-partum hemorrhage. I would like to emphasize the value of actual measurement. Those who have not done this will be amazed at the difference a forceps operation or an episiotomy makes in the blood loss. In that regard the low operative interference in this series is very commendable.

Our experience with ergonovine at The Florence Crittenton Hospital in Detroit is essentially the same as the essayist's. We have been using neogynergin which is ergotamine tartrate plus ergobasin, ergonovine being the name chosen by the American Medical Association for the water soluble oxytocic principle in ergotrate, ergometrin, ergobasin, and others.

The first method used by us called for the administration of 1 c.c. of ergonovine immediately following the birth of the baby. This was given in two ways, first intravenous, and then intramuscular. It was found in these cases that a contraction of the uterus would occur, clamping down upon the placenta and reducing the amount of blood lost in the third stage. Given at this time it was found that

frequently only a portion of the placenta would be sheared off by the action of the ergonovine and bleeding would continue until the one area which remained attached was completely separated. Some of these cases took as high as twenty-eight minutes to separate, with a considerable loss of blood. As a result, the average time for the entire series was a third stage of fourteen minutes and a blood loss of 400 to 500 c.c.

A different technique was then adopted in which 1 c.c. of ergonovine was given to the mother intravenously as soon as the anterior shoulder of the baby presented itself. Following the birth of the baby, the uterus was followed down and the placenta extruded as soon as possible. The adoption of this technique was followed by a drastic reduction in the time and the amount of blood lost in the third stage, compared with the previous method. In the second method, the mechanism of the third stage was changed so that instead of the placenta being separated by the formation of a retroplacental clot, it was separated by a shearing motion caused by the violent contraction of the uterus following the injection of the oxytocic drug. The average time of separation in this series was two and one-half minutes, the average loss of blood 125 c.c.

There were no actual retained placentas found in this group, but some placentas which had been separated and thrown down into the lower uterine segments were retained in that site and removed by extraction. Although we did not have any retained placentas in our series, the possibility of this occurring is still great. Another possibility that we must think of which at the present time has not been investigated is the possibility of a cotyledon of the placenta being separated and retained during the shearing process. The force of this shearing process was experienced in a manual removal of a portion of retained placenta when the injection was given and the hand withdrawn as the uterus began to contract down. The statement that shortening the third stage does not deserve serious consideration might be argued if we couple with it the fact that the longer the third stage, the greater the blood loss.

The author's conclusion is wise: that this procedure is not available for general adoption and I agree that, by and large, attempts to improve upon nature are not eminently successful.

DR. JAMES R. MANLEY, DULUTH, MINN.—Last year we ran a small series of 50 cases, using ergotrate intravenously and compared them with 50 cases in which ergotrate was given into the muscle after the placenta was expelled. We, too, found that with the former procedure there was a marked reduction in the amount of blood lost. We gave the ergotrate as soon as the anterior shoulder was born and we expressed the placenta within two or three minutes. We had no bad results, except one retained placenta.

We came to the same conclusions as the essayist, namely that it is not a procedure to be used in a general hospital, where oftentimes the intern is busy helping the obstetrician in a delivery by forceps and cannot be responsible for the giving of the ergotrate. Intravenous ergotrate is very valuable in post-partum hemorrhage and in cesarean section.

DR. R. E. ARNELL, NEW ORLEANS, LA.—During the past three years we have been investigating the effects of various oxytocic drugs on the third stage of labor. Blood losses were determined by an exact chemical-colorimetric method whereby the amount of hemoglobin loss (in grams) in free blood, clots, sponges and drapes, is converted into cubic centimeters of blood. This is a more exact method of determining blood loss than either clinical estimation, which is usually grossly inaccurate, or volumetric measurement (Pastore) of all fluid lost, which may include amniotic fluid and urine as well as blood.

The chart reveals our results in 500 consecutive normal cases (Table I).

TABLE I. EFFECTS OF OXYTOCIC THERAPY ON THE THIRD STAGE OF LABOR

	CASES	AVERAGES		COMPLICATIONS
		BLOOD LOSS IN C.C.	DURATION IN MINUTES	
No oxytocic	100	182	8.4	2 post-partum hemorrhage (over 500 c.c.) 3 excessive bleeding (300 to 500 c.c.)
Ergotrate intravenously with anterior shoulder	100	48	2.1	1 retained detached placenta (shoe-horn removal)
Ergotrate intravenously 1 min. after delivery of the baby	100	145	6.2	1 excessive bleeding (300 to 500 c.c.)
Pituitrin intramuscularly with anterior shoulder	100	106	4.5	None
Pitocin intramuscularly with anterior shoulder	100	78	4.4	None
Totals	500	111	5.1	

An evaluation of the results of intravenous administration of ergonovine with the delivery of the anterior shoulder of the baby may be summarized as follows:

Advantages.—

1. Diminishes blood loss during and after the third stage.
2. Lowers incidence of post-partum hemorrhage and the necessity for packing the uterus. The incidence of uterine tamponade on our service is now only one in 640 deliveries.
3. Shortens length of third stage, duration of anesthesia, etc.
4. Lowers incidence of infection.
5. Eliminates danger of individual susceptibility and anaphylaxis and can be used in the toxemias of pregnancy.

Disadvantages.—

1. Administration requires an assistant.
2. Good timing is necessary so that separated placenta can be expressed immediately.
3. Infrequent possibility of hour-glass contractions of uterus or spastic cervix requiring manual removal of placenta.
4. Danger of administering in case of undiagnosed twins.

DR. DIDDLE (closing).—Your personnel should be trained to the use of this drug. Every time we change interns the incidence of retained placenta increases. In the last six weeks we have had three out of 225 cases. When the intern becomes accustomed to its application, the incidence drops.

The use of ergonovine is to be continued indefinitely by us until a larger number of cases is collected to give more definite conclusions. Even though the drug may be recommended in large clinics it probably should not be made available in smaller institutions that have a limited personnel.

EFFECT OF LYMPHOGRANULOMA VENEREUM ON PREGNANCY, LABOR, AND THE FETUS*

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WHENEVER an infectious process occurs in a gravid patient, an understanding of the effect of the disease upon the product of conception and parturition, of the alteration of the course of the disease because of the pregnant state, and of the possibility of transmission to the fetus and newborn is apropos.

Lymphogranuloma venereum is rare in private patients, but more common in the charity services, especially among the colored race. The concomitant presence of lymphogranuloma venereum and pregnancy is striking because of its infrequency. Perhaps a few cases with minimal or no residual change remain undiagnosed. Within the past four and one-half years (Dec. 24, 1936, to June 30, 1941), 17 such patients have been observed at the Provident Hospital, whereas within the past ten years (May 25, 1931, to June 30, 1941) only one such patient has been diagnosed at the Chicago Lying-in Hospital. This rarity along with the infrequency of other pelvic neoplasms emphasizes the need for evaluation of the pelvis on prenatal examination, particularly in view of a few isolated reports which stress the possibility of tragedy at delivery both to the mother and the newborn. Nevertheless, the observations listed below do not agree with some references that termination before viability or in stillbirth is problematic merely because of this venereal disease damage. Perhaps during the active infection such hazards confront the fetus. More likely a relative sterility persists either because of pathologic alteration from an extensive inflammatory process of the disease or perhaps from other disease processes. It is not the rectal stricture as such that produces dystocia, but the associated perirectal hyperplastic or inflammatory reaction which obstructs the passage. The parturient uterus probably functions normally.

Repeated examinations before conception, during pregnancy, and after delivery have shown no noticeable alteration in the course of the disease or a change in the inflammatory tissue mass as a result of the pregnancy. All in this series were in the chronic or latent stages. Not one patient came to the prenatal clinic in the active state or developed an active process while under prenatal care. Possibly such stages did exist, but in any event the active stage went unnoticed.

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Whether the secondary state (systemic manifestation) of lymphogranuloma venereum would be associated with a different effect upon the fetus cannot be stated from our study or from the publications. Certain agreement may be found between this group and some reports that there is an increased abortion, premature labor, and stillbirth rate among women with this venereal disease. Even so exception must be taken because the data are from the histories prior to the pregnancies in question. As a matter of fact, the number that carried to term were well within the normally expected range. This may be challenged; first, for these prospective mothers may no longer harbor the virus and thus are free from the infection; second because early unintentional abortions may have occurred in many who did not seek obstetric care.

LITERATURE

Ample and adequate reviews on etiology, pathology, symptomology, diagnosis, treatment, and prognosis of lymphogranuloma venereum have come from the pens of Frei;¹⁵ D'Aunoy and von Haam;¹⁰ Torpin, Greenblatt, Pund and Sanderson;³¹ Kamouehi;²⁰ Buendia;⁸ Shrop-shear;²⁸ Stein;³⁰ Knight and David;²¹ Barber and Murphy;⁵ Coutts;⁹ and many others. Should the infections remain localized not much chance would exist for fetal involvement: but recently convincing evidence has been given which proves the possibility of systemic infection. Von Haam and D'Aunoy³³ reported the presence of the virus in the spinal fluid, but they were unable to indicate the incidence in which central nervous system infection may be expected. Gutman¹⁸ amplifies this point to the extent that systemic manifestations occur with sufficient frequency to be of general medical interest.

The present methods of demonstration of the virus in the blood stream of human beings serve inadequately, but Benedek and Olkon⁷ have confidence in the ultimate completion of this link. The systemic involvement and multiplicity of lesions are vouched for by Jones and Rome,¹⁹ Becker,⁶ Baneiu and Caratzali,⁴ and Kornblith.²²

The skin, bones and joints, eyes, throat, central nervous system, and other structures serve as a nidus and may become extensively injured. Thus the product of conception (the fetus and the placenta) must rely upon its own defense mechanism for its self-protection when its mother has a systemic involvement.

If the fetus acquires the infection it would surely show clinical evidence or give, after its birth, a positive reaction to the Frei antigen since in the adult the reaction is long standing if not permanent. Dick¹¹ emphasizes that the problem of transmission is unsettled although he reported one case with a positive reaction in an infant aged 2 weeks and again five months after birth. This last test gave a lesser response but with a weaker antigen. This reaction may result from passive transmission. Dick tested ten normal newborn infants to find negative reactions. Durel's¹³ investigation on 32 infants without clinical evidence of lymphogranuloma venereum produced all negative reactions. When compared to the 100 infants of Babonneix³ with only 3 transiently positive tests, much doubt may be cast upon the frequent likelihood of false positive tests and some assurance given to the contention of passive transmission of antigen reaction "bodies." More pointedly, Sonck²⁹

examined 19 children born of mothers who during pregnancy or parturition suffered with a process of lymphogranuloma venereum (termed active, but more likely residual or latent). The first 12 tested by antigens gave definite negative reaction. Two others had only detailed physical examinations, while the remaining 5 were examined, but not tested, by others.

The indisputable evidence of Dummer and Tamura,¹² Melczer and Sipos,²⁵ Sonck,²⁹ and Levy^{23, 24} established the juvenile or premenacmic* group and at the same time emphasizes that these are not congenital transmission but acquired infections after the natal day. These children developed the same types of syndrome as the adult.

The rarity of pregnancy occurring in a patient with lymphogranuloma venereum lacks complete explanation. Schutte and Lubitz²⁷ had no pregnancies in 17 patients with this disease. Gray and Barnes¹⁷ discovered 3 positive tests in 59 colored and no positive tests in 68 white prenatal patients. At the Provident Hospital, the incidence in pregnancy is approximately 0.5 per cent or roughly one in 200 out of 3,500 pregnancies, while in contrast at the Chicago Lying-in Hospital only one has been discovered in 27,000. Gray and Barnes raised the question whether there is some degree of sterility from the disease per se or whether these patients are sterile from other causes.

Not one reference is made to show that the maternal course of pregnancy was altered in the slightest. The wise and timely reports reveal that both maternal and fetal lives were lost because of the complication of pelvic obstruction at the time of delivery. Gaines and McDowell¹⁶ recommend abdominal delivery when sufficient obstruction prevails as one patient died after a rupture of the rectum into the peritoneal cavity from association with version and extraction after "failed forceps." R. E. Anderson² lost a patient because of a ruptured uterus in association with version and extraction in an attempt to deliver the fetus. Vignes³² states that not one of 12 women was able to bear a living child, as all attempts ended in stillbirth or neonatal death. An unexpectedly short labor in H. E. Anderson's¹ case in spite of the rectal stricture and perirectal mass eclipses the illumination of the foregoing. Even a single instance as Fagarasano's¹⁴ proves the possible danger of intestinal obstruction by rectal stricture during pregnancy. Michelson, Crotty and Kasselberg²⁶ stress that mothers with external lesions may give birth to babies physically normal and persistently test negative.

DATA AND COMMENT

Comparable to all clinical data many factors play their part in the summation. Not one maternal mortality occurred in these unselected 18 women. The syndrome of lymphogranuloma venereum as a complication of pregnancy was not recognized prior to 1936 at the Provident Hospital. The diagnosis was made by the presence of the syndrome and a positive Frei test.

The first abortion in the group was unintentional. The colostomy presumably had no bearing upon the interruption of the gravid state and presumably the disease was not the cause.

*Menaeme is defined by Dorland as "that period of a woman's life which is marked by menstrual activity." Premenacmic would be the adjective denoting the period prior to the menaeme. (H. C. H.)

The second abortion and the first therapeutic one was done because of a severe anemia and generally very poor condition. Post-partum sterilization protected against a repetition.

The third gravid patient in which this complication occurred had had a complete obstruction of the bowel relieved by a colostomy before conception in which this complication occurred. The pelvic cavity was decreased slightly by the tissue reaction. Because of the possible need for abdominal delivery in the presence of a colostomy opening, the pregnancy was terminated, but sterilization was deferred in the hope that enough improvement would take place in the rectum to permit closure of the colostomy. If then a pregnancy occurred and abdominal delivery became necessary, it could be done with greater safety theoretically. The next pregnancy occurred about one year later but the patient postponed coming to the prenatal clinic until the last trimester. The pregnancy proceeded normally to term without symptoms even with the bowel fixed at the colostomy opening and during the ensuing labor. The inflammatory tissue yielded sufficiently for normal vaginal delivery.

The two patients with colostomies (carrying their pregnancies to term) had a normal parturition and convalescence. Twice cesarean section was employed to accomplish the delivery, both times because of frank obstruction by "soft" tissue masses. The most severe one (4) had fixed pelvic mass above an extensively necrotic vaginal wall and had externally a pronounced elephantiasis of the vulva. The second patient (5) presented the mechanical blocking without the destructive process.

In Case 7, an extensive fecal impaction above the rectal stricture prevented the presenting part from entering the true pelvis. By means of dilatation of the rectal stricture and repeated enemas the fecal mass was removed after which normal descent and delivery of twins took place. The only forceps delivery was in the white patient at the Chicago Lying-in Hospital (1940). This low forceps operation was indicated for other conditions than those resulting from the process of the lymphogranuloma venereum.

These 18 mothers (17 colored and 1 white) received obstetric care in 21 gestations during this study. Two therapeutic and one unintentional abortions account for the 3 losses of fetal life. Two mothers each had repeat pregnancies going to term uneventfully under these observations, while one had twins.

These same 18 mothers had 58 pregnancies in all, 21 of which came under this study directly. There were 37 prior to the first visit. From this number, abortions, stillbirths, and neonatal deaths, a total of 11, reduced the number of living fetuses to 27. One of the four abortions was induced. The 6 stillbirths and neonatal deaths are without explanation. The abortion rate is within the expected range but the loss of life, because of prematurity or other causes, is abnormally high. This finding agrees in part with certain contentions that one should anticipate this in these cases, but lacking specific information such a deduction is not justified.

The gestations under study carried to or near term and culminated in 19 living births (no stillbirths or neonatal deaths). All 19 babies were tested intradermally with at least one or more known dependable antigens from human sources. Twelve newborn infants were tested with mouse brain antigen and mouse brain control as well as with

TABLE I

PATIENT	AGE	PREGNANCY PRIOR TO GESTATION IN QUESTION				LESION AND OTHER COMPLICATIONS	DELIVERY	BABY
		*TOT.	LIV.	S & N	ABORT.			
Abortion—Therapeutic and Unintentional								
1	35	1	1			Rectal stricture; Colostomy	Abortion unintentional	
2	28	3	3			Rectal stricture; anemia, poor condition	Therapeutic abortion; sterilization	
3	31	1			1	Rectal stricture; fistula; Colostomy	Therapeutic abortion	
Normal and Operative Deliveries								
4	23	4	3		1	Rectal stricture; vaginal slough; syphilis	Cesarean section	Normal
5	26	2	1	1		Rectal stricture; pelvic mass	Cesarean section	Normal
6(W)	40	1	1			Rectal stricture; fistula; heart disease	Low forceps	Normal
7	32	1	1			Rectal stricture; fecal impaction	Normal—twins	Normal
3	33	+1			+1	Rectal stricture; fistula; colostomy	Normal	Normal
8	23	0				Elephantiasis; vulval and vaginal ulceration	Normal	Normal
8	25	+1	+1			Vaginal scarring	Normal	Normal
9	33	4	3	1		Rectal stricture; fistula	Normal	Normal†
9	34	+1	+1			Rectal stricture; fistula	Normal	Normal
10	26	4	3	1		Rectal stricture; condyloma; syphilis	Normal	Normal
11	26	3		3		Rectal stricture	Normal	Normal
12	24	0				Rectal stricture; elephantiasis	Normal	Normal
13	30	4	3		1	Rectal stricture; colostomy	Normal	Normal
14	30	0				Rectal stricture; fistula	Normal	Normal
15	32	1	2 (twins)			Rectal stricture	Normal	Normal
16	32	2	1		1†	Rectal stricture	Normal	Normal
17	37	1	1			Rectal stricture	Normal	Normal
18	.	2	2			Rectal stricture	Normal	Normal
Total		37	27	6	5	18 patients: 21 pregnancies; 22 fetuses 19 term; 3 abortions		

*Tot., total; liv., living; S & N, stillbirths and neonatal deaths; abort., abortion; W., white; +, add one more to total first listed for given patient.

†Induced abortion.

‡Baby gave positive Frei reaction on third and tenth days only.

human test materials. These were made within the first ten days of life on 13 babies born from 10 mothers (2 repeat pregnancies and one twin pregnancy). Only one baby out of 13 gave a positive test and these readings were made on the third and tenth days. Even this infant had a negative test within three months, and it has since remained negative. All babies were completely or partially breast fed by their mothers. Therefore breast feeding was apparently safe in these 19 instances.

All 19 are clinically free from the disease and appear physically and mentally normal.

It is pointed out that all of these mothers were apparently in the latent stage of the disease, and therefore probably noninfectious. If this is correct, and it appears that it is, then the hazards to reproduction involve first the consideration of whether the residual damage produces a sterility. No evidence is at hand on this point. Although skin tests have not been made, clinical evidence points out that sterility is not a part of the picture. Next, if conception occurs what may happen to the product of it. Thus far it seems safe to predict that it is safe for the fetus during latency. The mothers were not made worse nor was the process obviously altered. Labor began at or near the end of pregnancy (within normal range limits) and pursued its usual course successfully unless the birth canal was insufficient.

Only 7 placentas were examined microscopically. The histologic pattern was normal in all which is in accord with the gross appearance of the entire series.

It would be worth while indeed to find a sufficient number of pregnant women who had the disease in the active phase, particularly if one could prove a systemic manifestation in them. If this virus passed through the placenta, much damage could result, but again the fetus, like its mother might have little or no residual damage. If, on the other hand, the damage was severe, extensive or lethal, an abortion or stillbirth could be expected.

All pregnancies continued without special therapy for the venereal disease. Sulfanilamide has given some responses but most in the active or early latent stage. When the indication arises this drug could be given during the pregnancy.

CONCLUSIONS

The findings from this small number become more impressive when the infrequency of the disease of lymphogranuloma venereum in association with pregnancy is recognized. Tempting though it is, specific deductions must be guarded against until confirmation appears.

1. The common occurrence of pregnancy and the acute phase (systemic manifestation) must be extremely unlikely.

2. It remains unsettled what results may follow for the fetus or for the mother if an active infection is acquired during pregnancy.

3. Sterility is not necessarily related to the disease unless it resulted from a reaction in the gonads, tubes, or uterus, which seems to be unlikely.

4. The pregnancy should be carried to term unless therapeutic abortion becomes indicated for an obstetric or medical reason.

5. Colostomy may offer technical difficulty either in a possible obstruction or by contamination at delivery particularly if one resorts to cesarean section.

6. Pregnancy per se did not alter apparently the course of the disease.

7. There is the possible hazard of mismanaged labor if the pelvis is obstructed.

8. Nineteen babies born of and breast fed by mothers with a latent lymphogranuloma venereum have been normal and free from the disease.

9. Only one baby in 13 showed any evidence of passive transfer of antigenic bodies. In spite of 2 positive tests (on third and tenth days), the tests became negative within three months and so remained.

10. Tests in the newborn should be made with known dependable antigens and with more than one antigen. Tests shortly after delivery and again months later are indicated.

11. The placentas appeared normal grossly and the few examined microscopically showed no characteristic alteration.

12. It is hoped that others interested in this field will make observations in all stages of lymphogranuloma venereum for evidence of transmission to the fetus in utero or at parturition.

Dr. Edward W. Gray's assistance in examination of the infants is greatly appreciated.

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DISCUSSION

DR. EDWIN L. ZANDER, NEW ORLEANS, LA.—We have made a study of the cases of lymphogranuloma venereum in Charity Hospital in the past two years. There were five cases on the colored service in 7,685 deliveries and none on the

white service in 3,973 deliveries. All women were delivered of live babies weighing from four to six and one-half pounds, with an average weight of five pounds one ounce. The six and one-half pound case required an episiotomy which was sutured with silkworm and healed without difficulty. Three of the five cases terminated thirty-two to thirty-six weeks and the other two at term. There was no record of any abortions in patients with lymphogranuloma venereum. We have noticed in one case an increase in the size of the vulvar masses during pregnancy.

The danger of delivery from below lies first in the possibility of trauma at delivery, and second, in the danger of puerperal morbidity. In four of these five cases morbidity was present.

A positive Frei test does not mean that active infection is present but that at one time the patient may have been infected. We must emphasize that the clinical picture must conform to the disease in order that a positive Frei may be accepted as of value. We have seen cases in which all the venereal diseases were present in one patient and for this reason a careful differential diagnosis is necessary, especially between lymphopathia venereum and granuloma inguinale. There have been delivered in this same period at Charity Hospital, ten cases of granuloma inguinale of which six had syphilis also.

All the babies born are at present alive and have shown no evidence of the disease. It seems possible, however, that, in cases of pregnancy with active disease, fetal infection could occur, for we know of a case reported by Dr. R. E. Arnell and diagnosed by Dr. J. K. Howles in which granuloma inguinale of the umbilicus occurred after delivery from below.

It does not seem that sterility per se is a part of the disease as witness the eighteen cases reported herewith, plus the five cases we have had in the past two years. Naturally sterility from occlusion of the vaginal tract is possible. The vaginal tract itself is not frequently involved because of poor lymphatic system, as this is essentially a disease of the lymphatic system.

DR. F. J. TAUSSIG, ST. LOUIS, MO.—Dr. Hesseltine's paper brings up the general problem of vulvar lesions complicated by pregnancy. We have in cases of granuloma venereum a condition of the external genitals, particularly of the rectovulvar septum, that presents a serious danger at childbirth. My experience dates back many years before the time when this disease was recognized as an entity and when we were still calling it tertiary syphilis. In my City Hospital service in these years I recall approximately three cases, one of which was permitted to deliver from below without any special precautions. It resulted in a tear of the rectum and a stenosis that killed the patient. Where the disease is fairly well under control, it seems to me that the possibility of delivery from below is to be considered, provided we do not let the head go down on the pelvic floor, but proceed at once, after complete dilatation of the cervix, with a high perineotomy. This should be so high as to relieve all pressure against the rectovaginal septum, which, if involved, is likely to break through and cause a rectovaginal fistula. In cases of extensive involvement cesarean section is definitely indicated.

May I say just a word as to the tendency to do cesarean section in patients who have had a previous vulvectomy for leucoplakic vulvitis or carcinoma of the vulva. I have had several cases in this classification and I would say that cesarean section is practically never indicated, particularly if at the time of the vulvectomy care is taken to bring down a flap of the posterior vaginal wall, thus producing, at least in appearance, the condition of a second degree tear at the end of the operation. By bringing down the flap of the posterior vaginal wall, we prevent the stricture that otherwise results, and if in such cases we do a high perineotomy, we can apply forceps and obtain delivery without any complications from below.

DR. H. E. ANDERSON, OMAHA, NEB.—In 1939 we had one of these problems, which has been reported. The patient was a colored girl who had had a perirectal mass for a number of years during which time she had been delivered of two children. She had this very large perirectal mass when she came to us and also a slight elephantiasis of the vulva. While we were debating whether she should be sectioned, she underwent what was practically a precipitate delivery.

DR. HESSELTINE (closing).—In our series the morbidity was the same average as for the entire obstetric series. I might point out that these cases did not have much sloughing of the vaginal structures or, with one or two exceptions, open lesions. The worst one was a patient who had a therapeutic abortion and sterilization because of extensive vaginal sloughing. The others had a latent or a more or less completely healed process. It would be most interesting to learn what would be the results to the fetus if a systemic process developed.

NUTRITIONAL EDEMA IN PREGNANCY*

WITH AN ANALYSIS OF EIGHT SEVERE CASES

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IN THE course of an extensive study carried out in the obstetric clinics and wards of Charity Hospital of Louisiana at New Orleans we have observed in considerable detail approximately 500 women who presented marked degrees of edema. In every instance the edema was too extensive to be classified as the type which appears so constantly in pregnancy that it might almost be described as physiologic. In the majority of instances it could be readily explained on the basis of cardiac or renal disease or the toxemias of pregnancy. In some instances it could be explained on the basis of miscellaneous causes, chiefly inflammatory or mechanical, such as thrombophlebitis, angioneurotic edema, or varicose veins. In a small group of cases the edema, which was very extensive, could not be explained on the basis of any of these causes.

In every one of the cases in this special group, a common factor of hypoproteinemia could be demonstrated and could be clearly attributed to protein malnutrition. In other words, the patients in this small group presented the type of edema which is classified as nutritional and which is due, alone or in combination, to an inadequate protein intake or to a deficient absorption or utilization of ingested protein.

The purpose of the present communication is to consider the association of nutritional edema and pregnancy, both in general and with particular reference to eight carefully studied cases in which the edema was

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of a very marked degree and was apparently conditioned primarily by a hypoproteinemia due to one or more of the causes listed.

A voluminous literature has accumulated concerning water balance and edema in pregnancy, and the nutritional aspects of maternal care have recently received a great deal of attention, but, so far as we have been able to ascertain, nothing at all has been published on the subject of nutritional edema in pregnancy. This is curious since, according to experienced workers in this field, nutritional edema is actually more frequent on the obstetric than on the medical services of most hospitals.

Historical Note.—The scientific study of edema due to malnutrition dates from 1865, in which year Cornish (cited by Nixon¹) published his observations on the condition in India, where widespread famine had affected large portions of the population. As a matter of fact, this type of edema had been known for hundreds of years earlier and had always been associated with war or famine.

The Bible mentions the "hunger swellings" and "bitter end" of people suffering from famine after drought. In the fourth century B.C. the philosopher Heraclitus, according to Diogenes Laertius (cited by Youmans²), died of dropsy because he lived on a diet composed entirely of vegetables and herbs. Jovius wrote of the French army fighting before Naples in 1528, "Those starved soldiers who were not confined to bed were seen with pallid faces, swollen legs, and bloated bellies, scarcely able to crawl." Dozens of similar references might be cited in this connection.

The modern interest in nutritional edema dates from World War I, when, following the reduction of essential food supplies, numerous instances were reported, first in prison camps and devastated areas, and later in the general population. The first cases were observed at Lille, after the Germans, in 1914, had occupied the town and stripped it of its supplies. In 1918 Schittenhelm and Schlecht reported 200 cases from a single prison camp, and other large series were reported in that year and in the years immediately after the war.

In civil life nutritional edema has been reported from India, China, Ireland and Mexico, and has involved large proportions of the populations during periods of famine. It has been observed, in the absence of famine, in individuals with deficient diets, and is so frequent among the poorer classes of the United States that, according to Youmans,⁴ it amounts to a public health problem.

Nutritional edema has long been recognized as a prominent clinical feature of such diseases as beriberi, scurvy, pellagra, typhus, dysentery, and malaria. When it appears in this association, some authors believe that it represents a special type of the particular disease with which it is associated.

Cornish stated that nutritional edema was a definite disease entity caused by a deficiency of nitrogenous foods. Many authors pointed out the association between the edema observed during the last war and the deficient diets prevalent then. Falta (cited by Youmans²), in 1917, stated that in the districts in which the disease was observed meat was frequently unobtainable for months at a time, and large

amounts of salt and water were ingested in an attempt to supplement the bread and thin vegetable soup which formed the chief items of the diet. Schittenhelm and Schlecht also noted the association between an excessively "wet" diet and edema. From the laboratory standpoint, Maver,⁵ Schittenhelm and Schlecht, Falta and others studied the protein deficiency in the diet. Falta observed that the protein intake of the subjects whom he studied averaged less than 15 Gm. per day, and Maver found the serum protein of the blood low in instances of war edema. It was not until the past decade, however, that extensive clinical and experimental studies have clearly shown that the immediate cause of edema in these cases is a hypoproteinemia due to protein malnutrition of various origins.⁶⁻⁹

Maver, in 1920, was the first to recommend the term "nutritional edema" which is now in general use. Prior to that time the condition has been described by such terms as "famine edema," "war edema," "prison dropsy," "starvation dropsy," and "hunger swelling," all of which indicate the circumstances under which the edema may occur but give no hint of its etiology, as does Maver's nomenclature.

PATHOGENESIS AND ETIOLOGY OF EDEMA

Although much concerning the etiology and mechanism of nutritional edema remains to be elucidated, certain general statements concerning edema are applicable to this special variety, and are also applicable to nutritional edema in pregnancy. The special factors operative in pregnancy will be discussed under a separate heading.

Generally speaking, any type of edema occurs as the result of a complex mechanism dependent primarily on the following factors, which may occur alone or in combinations of two or more: (1) A decreased colloid osmotic or oncotic pressure of the plasma proteins, (2) an increased capillary permeability, (3) an increased capillary blood pressure, (4) a decreased lymphatic drainage and a decreased tissue pressure.

Nutritional edema is due to a protein deficit caused, as has been pointed out, by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. Other causes also play more or less important roles. Anemia is very commonly found in association with the hypoproteinemia in such cases. Secondary or contributory factors include hot weather, overwork, the excessive ingestion of salt and water, the dependent position, and decreased elasticity of the tissue spaces. The effect of these various factors upon the mechanism responsible for edema should be briefly discussed.

Serum Protein Concentration and Colloid Osmotic Pressure.—The serum protein concentration of the blood chiefly determines its colloid osmotic pressure. Serum proteins are therefore the determining factors in the distribution of extracellular fluid. Albumin plays a more important role than globulin, because its osmotic effect is approximately four times greater.

Edema is likely to occur whenever the colloid osmotic pressure of the serum proteins is less than 20 cm. of water, at which level the serum protein concentration is usually less than 5.5 Gm. per cent and the serum albumin concentration is less than 2.5 Gm. per cent. On the other hand, no categoric statements can be made concerning the level at which clinical edema will appear; because of the variability of the other factors taking part in the phenomenon, there is no critical level of serum protein concentration, and each case must be studied individually. In serial determinations on a large number of pregnant women, we have frequently observed values as low as 4.9 Gm. per cent without associated pitting edema or abnormal weight gains.

Although nutritional edema is beyond question due to the adverse effects of a protein deficit, however it may be caused, on the osmotic balance, the so-called "lack loss" theory is an over-simplification of the subject. It does not, moreover, explain all cases, as various authors have pointed out. Whipple¹⁰ has suggested that the liver may be concerned in a specific mechanism for the regeneration of plasma proteins, and that this mechanism may be disturbed by severe hepatic disease with resulting perversion of hepatic function. Such a theory would be supported by our recent observation of a case of acute yellow atrophy of the liver in pregnancy, in which the serum protein concentration did not at any time rise above 2.6 Gm. per cent, in spite of a very high protein intake and repeated blood transfusions. Casten and Bodenheimer¹¹ mention a similar case.

Relationship of Edema and Anemia.—It is now well known that severe anemia may cause edema, either per se or in association with hypoproteinemia. Peters and his associates⁷ have demonstrated that when the two conditions co-exist, the edema will appear at higher protein concentrations than when hypoproteinemia alone is present. The mechanism of the production of edema associated with anemia is not clearly understood, though the anemia, as under all other circumstances, is caused by a deficiency in either the protein or the iron of which the hemoglobin molecule is composed.

A reasonable supposition is that an oxygen deficit may play a part. Casten and Bodenheimer pointed out that the anoxemia resulting from severe anemia may affect adversely the structures concerned with the synthesis of plasma proteins, producing, in turn, a hypoproteinemia and a decreased colloid osmotic pressure.

That anemia may be responsible for the appearance of edema, without an associated hypoproteinemia, is evident from the following cases which are of particular interest:

A white woman, 34 years of age, para vi, was admitted to the New Orleans Charity Hospital in the sixth month of pregnancy, suffer-

ing from hookworm associated with massive edema. The blood pressure was 135/90. The urinalysis revealed nothing abnormal. The initial examination of the blood revealed 910,000 red cells per c. mm. The hemoglobin value was 2.4 Gm. per cent and the cell volume 10.2 volumes per cent. The serum protein concentration was 6.4 Gm. per cent.

The patient received in all nine transfusions, totaling 5,150 c.c. of whole blood. Laboratory studies twenty-four hours after the second transfusion showed all the blood values elevated over the initial values. The red blood cells now numbered 1,680,000 per c. mm., the hemoglobin determination was 4.1 Gm. per cent, the cell volume 17.5 volumes per cent, and the serum protein concentration 6.8 Gm. per cent. Clinical improvement paralleled the laboratory improvement. Within twenty-four hours after the second transfusion the patient passed 6,200 c.c. of urine, and her weight loss in twenty-two days amounted to 17 kg. (37.4 pounds).

In this case the anemia was clearly the important factor in the abnormal water retention, and it is of interest to note the relatively small increase in hemoglobin, red cell count and cell volume which initiated the diuresis, weight loss, and general clinical improvement. Dieckmann¹² has also observed edema in a number of pregnant women who had serum protein concentrations well above the level at which edema would be expected to appear but all of whom exhibited varying degrees of anemia. In his cases edema was present when the hemoglobin values ranged from 3 to 8 Gm. per cent, but disappeared when the values had been increased to 11 Gm. per cent by blood transfusions.

On the other hand, too much should not be read into such cases, since anemia is not necessarily associated with edema or abnormal weight gain. We have observed several cases, for example, in which marked degrees of anemia, in one instance with a hemoglobin value of 4.4 Gm. per cent, was not associated with either of these findings.

Furthermore, when hypoproteinemia and anemia are associated, the hypoproteinemia may be the fundamental deficiency, as the following case (Table I), in which a deliberate therapeutic test was carried out, clearly shows:

A white woman, 31 years of age, para vi, was admitted to the New Orleans Charity Hospital in the eighth month of gestation, with massive edema of the extremities and trunk, which had been present for ten days. She also had a marked anemia and hypoproteinemia. For the first seven days of hospitalization general supportive measures were carried out, including bed rest, a high-protein, salt-poor diet, parenteral vitamin therapy, and intravenous hypertonic dextrose infusions. The response to these measures was slight. During the next six days the patient was given three transfusions of washed red blood cells. The anemia was strikingly benefited, but the edema was not materially improved and the serum protein concentration was only slightly altered. The patient was then given one transfusion of plasma and two of whole blood, which were followed by prompt results in respect of diuresis, improvement in and finally disappearance of the edema, and a loss of weight which by delivery had amounted to 16 kg. (35.2 pounds).

TABLE I. DEMONSTRATION OF ETIOLOGIC FACTOR (HYPOPROTEINEMIA VERSUS ANEMIA) IN CASE OF NUTRITIONAL EDEMA BY EFFECT OF VARIOUS THERAPEUTIC MEASURES

DATE	SERUM PROTEINS*		BLOOD			WEIGHT IN KG.	THERAPY
	TOTAL	ALBUMIN	CELL VOLUME	HEMOGLOBIN*	RED BLOOD CELLS†		
8/13/40	4.5	2.2	28.6	7.7	2.85	73.0	Bed rest, high-protein, salt-poor diet, diet, intravenous dextrose (20%), vitamins B ₁ and C. Edema unchanged
8/15/40	4.4		26.0	7.5		73.5	
8/19/40	4.9			7.7		72.0	
8/20/40						71.0	Transfusion (red blood cells only, 250 c.c.)
8/21/40							Same (300 c.c.)
8/25/40	4.8	2.5	30.2	8.8	3.10	70.4	Same (250 c.c.)
9/ 1/40			32.9	9.4		68.8	Edema practically unchanged
9/ 3/40			32.5	9.0	3.65	69.0	Transfusion (plasma only) 250 c.c.
9/ 5/40			31.6	8.8		66.1	Edema improved
9/ 9/40	5.0					64.0	Transfusion (whole blood, 650 c.c.).
9/10/40							Edema improving
9/14/40							Transfusion (whole blood, 500 c.c.).
9/14/40	5.8	3.2	34.2	10.2	4.10	57.6	Edema improving
9/27/40	6.9		37.4	11.0		57.0	Edema entirely gone
							Delivery

*In Gm. per cent.

†In millions.

Contributory Causes of Edema.—The influence of certain contributory causes of nutritional edema may be briefly mentioned. The observation that latent or mild edema becomes much more marked on very hot days is explained by the fact that in hot weather there is always peripheral vasodilatation, an elevation of the capillary blood pressure, and, as a result of capillary dilatation, an increase in the area of the capillary wall available for filtration, all of which add up to a disturbance of osmotic balance. This observation, as might be expected, is very common in the prenatal clinics of the New Orleans Charity Hospital.

The importance of an increased intake of salt and water, or their impaired elimination, or both, is now so well known in the pathogenesis of edema as to require no amplification. These factors, like the one just mentioned, are of unusual importance in the South, where highly seasoned food is the rule and where the ingestion of large amounts of salt, at times as high as 30 or 40 Gm. per day, is not at all uncommon and is an obvious source of danger for patients with potential or actual edema.

Another possible source of danger for such patients is found in what amounts to baking soda addiction. Among negroes in particular, baking soda is a household remedy, taken orally on all possible occasions, and pregnant women sometimes consume incredibly large amounts.

Both the dependent position of the extremities and strenuous physical activity of any kind increase the tendency to edema by increasing the capillary blood pressure. As Keys and Taylor¹³ have pointed out, the hemoconcentration which occurs during activity is the result of filtration of fluid of low protein content from the blood into the tissues.

One of our patients stated that she had had only mild edema until she spent several days on her feet in a hot kitchen cooking and baking in preparation for her daughter's wedding. In another case the effect of dependency on both hematocrit and serum protein concentration could be demonstrated in the laboratory.

A colored woman, 28 years of age, para iv, presented a massive edema of the trunk and lower extremities for which a high Fowler position was necessary. Blood from the veins of the foot revealed the serum protein concentration to be 5.0 Gm. per cent, as compared with 4.1 Gm. per cent for the veins of the arm, and the hematocrit value to be 38.8 Gm. per cent for the veins of the foot as compared with 30.8 Gm. per cent for the veins of the arm.

NUTRITIONAL EDEMA IN PREGNANCY

The general statements which have been made concerning edema in general and nutritional edema in particular naturally apply to preg-

nancy also. In this state, as in any other state, hypoproteinemia may develop from an inadequate intake of protein, a deficient utilization of protein, or an excessive loss of protein because of vomiting, diarrhea, or proteinuria. Anemia and the other causes which have been discussed play parts of varying importance. Certain peculiarities of the pregnant state may also be mentioned.

Among these peculiarities are the physiologic alterations found in the latter part of pregnancy, which include, in addition to the mechanical effects of the enlarging uterus, an increase in blood volume amounting to 25 per cent; a decrease in plasma protein of 5 per cent; an increase in cardiac output of 50 per cent; and a moderate elevation in venous pressure.

Burwell¹⁴ has demonstrated that the pitting edema of the ankles, usually found to some degree in most pregnant women late in gestation, may be attributed to increased venous pressure. According to Davis,¹⁵ even a normal pregnancy is accompanied by a positive water balance, the fluid retention being most pronounced in the last trimester.

Melnick and Cowgill,¹⁶ as the result of experiments on pregnant dogs, state that protein reserves are always decreased in pregnancy, that fetal demands on the maternal organism are always high, and that the mechanism of protein synthesis and regeneration is almost routinely impaired.

If these observations could be confirmed on human subjects, they would be an extremely important contribution to the subject of nutritional edema in pregnancy.

Site of Edema.—Under all circumstances the site of the edema is determined by the elasticity of the tissue spaces in various parts of the body. For this reason, as well as because of the mechanical conditions incident to pregnancy, the vulva, the tissues of which are very loose, is likely to become markedly edematous very rapidly.

In one instance of nutritional edema which we studied (Fig. 1), the vulvar edema was so marked that clear fluid could easily be withdrawn for chemical analysis. The local serum protein was 0.65 Gm. per cent and the chlorides 690 mg. per cent, as compared with the blood serum protein of 3.6 Gm. per cent, and the blood chlorides of 486 mg. per cent. The chlorides, which normally are only 40 or 50 mg per cent higher in the cellular spaces than in the blood, in this instance showed an increase of 204 mg. per cent.

This is a striking demonstration of the increased permeability of the capillaries to salt and water in pregnancy.

Dietary Deficiencies.—A protein deficiency might be expected in obstetric patients of the lower social stratum, but an investigation which we recently carried out on 100 pregnant women admitted consecutively to the prenatal clinics of the New Orleans Charity Hospital revealed deficiencies which were nothing short of startling. Almost without ex-

ception the diets were found to be deficient in proteins, minerals, and vitamins. The highest sustained protein intake was 1.4 Gm. per kg. of body weight per day, and the mean intake was 0.78 Gm., which is less than half the optimum intake for pregnancy (estimated at 1.5 to 2 Gm. per kg. per day for the last trimester of pregnancy). Sixty-eight per cent of the patients had intakes below the safe minimum and intakes of 0.3 Gm. per kg. per day were not at all unusual. With subclinical dietary deficiencies of such a degree, it is surprising that nutritional edema is not observed more frequently.

It must not be forgotten that dietary deficiencies are frequently present in private patients in easy financial circumstances. Patients of the poorer classes restrict their protein intake because foods which supply proteins of high biologic value cannot be secured on their limited in-



Fig. 1.—Case L. B. (Hospital No. L-48736.) Massive edema of the vulva in case of nutritional edema in pregnancy.

comes. Private patients restrict their diets because of food fads or actual or supposed idiosyncrasies to certain foods. In some instances the protein intake of pregnant women is still being restricted because of the idea, now completely disproved, that a high proportion of protein in the diet is likely to cause toxemia.

ANALYSIS OF CASES

Criteria of Selection.—The eight cases studied in detail upon which this paper is based were selected by criteria which were made deliberately high, in order to exclude questionable or borderline cases. These criteria included:

1. Absence of cardiac or renal disease, the toxemia of pregnancy, or any similar condition in which edema is a very frequent finding.

2. The presenee of an obvious, deeply pitting edema of the lower extremities and vulva.

3. A minimum weight loss of 7 kg. (15.4 pounds) from the beginning of treatment to the day of delivery. The weight loss specified was selected arbitrarily, and was purposely made high, to avoid the criticism that it might have occurred as the result of other factors than loss of water. As a matter of fact, the weight loss was always greater than it seemed, since no allowance was made for the gain in weight which would normally be expected late in pregnancy.

Age, Parity, Race, and Stage of Gestation.—The youngest patient in the series was 26 and the oldest 41 years of age; the average age was 33 years. All the patients were multiparas, the parity ranging from 3 to 11 pregnancies. Observations on these and other groups of patients leave no doubt that the tendency to protein malnutrition is increased by the strain of repeated pregnancies in rapid succession.

The figures are too small to permit conclusions, but it may be mentioned that the predominance of white patients (5 white, 3 colored) may be significant, since 65 per cent of the obstetric admissions to the New Orleans Charity Hospital are colored patients. It seems reasonable to assume, in view of other information we possess concerning this race, that colored women, because of their habitually unbalanced diets, are more resistant than white patients to dietary defects during pregnancy.

In all 8 cases the edema was first noted in the last trimester of pregnancy. The stage of gestation when the patients were first seen was between twenty-nine and thirty-seven weeks, and the average duration was thirty-three weeks. The final trimester of pregnancy would be the logical time for nutritional disturbances to appear, since it is the time when both maternal and fetal requirements are highest.

Clinical Findings.—Edema was the only finding common to all cases, and in cases uncomplicated by other diseases or conditions was always the chief complaint. Weakness and dyspnea were observed frequently but not uniformly, and whether or not they were present seemed to depend upon the degree of edema or the presence of associated diseases. Physical examination, except for the edema, was essentially negative in every case.

All the patients had had edema of mild degree for several weeks, but the massive edema which brought them to the hospital appeared suddenly. It should be emphasized that none of them had ever had severe edema prior to its development at this time, and that the edema has not reappeared in any instance since the pregnancy, although the follow-up has been for periods ranging from six months to two years.

All of the patients had massive edema involving the lower extremities and trunk, and in some instances the upper extremities and face also. In every instance the edema about the vulva was particularly annoying.

It is a matter of interest that none of these patients contrary to the experience of others, who have studied hypoproteinemia, developed either ascites or pulmonary edema. Casten and Bodenheimer¹¹ point out that the lungs are so frequently involved in this type of edema as to seem a site of predilection.

The blood pressure was slightly elevated in two instances, to 150/90 and 148/85, respectively, and all the patients had rapid pulse rates when they were admitted to the hospital. The hypertension and elevation of the pulse rate promptly disappeared after the patients had been in bed for several hours, and could reasonably be attributed to the effects of dependency and physical activity, plus the increased effort required to move the swollen extremities.

Laboratory Findings.—Two patients had heavy traces of albumin in the urine, which disappeared soon after they were admitted. Urinalysis was essentially negative in the other six cases. Blood chemistry determinations, including urea nitrogen, nonprotein nitrogen, sugar, chlorides, cholesterol, and carbon dioxide-combining power, were all within normal range for the stage of pregnancy. Gastric analysis was carried out in three cases, one of which exhibited a hypoacidity. The Quick hippuric acid test revealed no hepatic dysfunction in the single case in which it was carried out. Roentgen ray examination of the chest and heart and electrocardiography revealed no significant findings. Examinations of the eye grounds were uniformly negative.

Anemia was present in every case, being of the hypochromic variety in six and of the hyperchromic variety in two.

Hypoproteinemia.—For all practical purposes, all of the findings mentioned, except the blood studies, were negative. On the other hand, studies of the serum protein concentration revealed it to be low in all eight cases (Table II), the principal decrease being in the albumin fraction. Calculations of the colloid osmotic pressure of the serum protein¹⁷ gave values in all cases well below the level at which edema would be expected to appear.

TABLE II. SERUM PROTEIN VALUES AND COLLOID OSMOTIC PRESSURES IN EIGHT PREGNANT WOMEN WITH MARKED NUTRITIONAL EDEMA

CASE	SERUM PROTEINS*			ALBUMIN- GLOBULIN RATIO	COLLOID OSMOTIC PRESSURE†
	TOTAL	ALBUMIN	GLOBULIN		
1	3.0	1.6	1.4	1.14	9.3
2	3.6	1.8	1.8	1.0	11.6
3	3.8	2.1	1.7	1.23	12.9
4	4.1	2.0	2.1	0.95	13.7
5	4.4	1.9	2.5	0.76	14.5
6	4.5	2.2	2.3	0.96	15.6
7	4.8	2.5	2.3	1.08	17.5
8	5.4	2.2	3.2	0.70	18.6
Mean	4.20	2.03	2.16	0.94	14.21

*In Gm. per cent.

†Calculated in cm. H₂O by formula of Wells and others.¹⁷

2. Dextrose infusions were given, for their nutritive value, their effect on the liver, and their diuretic effect. Diuretic drugs have not proved effective in our hands.

3. Vitamins B₁ and C were administered parenterally, on the empiric basis of possible deficiencies of these accessory factors in the diet, such deficiencies have not been proved in nutritional edema, but some observers still believe vitamin therapy to be of value.

4. When swelling about the vulva was a source of great discomfort, as it was in several cases, temporary relief was obtained by puncture of the swollen labia, under strict aseptic precautions.

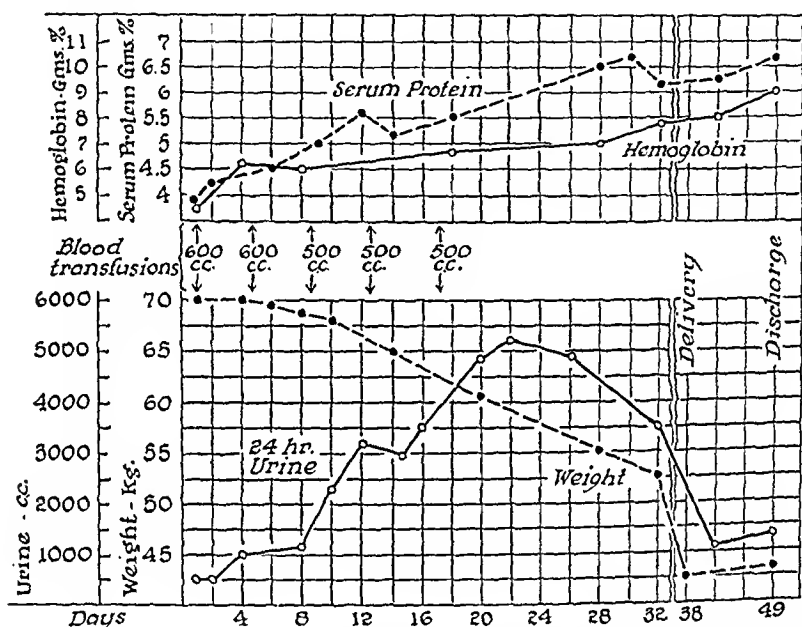


Fig. 2.—A. E. (Hospital No. L-40-15460.) Graph illustrating the typical response in weight loss, polyuria, increased serum-protein concentration, and hemoglobin value, following repeated whole blood transfusions in nutritional edema.

5. A high protein diet was instituted in all patients in whom digestive disturbances did not contraindicate oral feeding. Regardless of the digestive status of the patient, however, extreme protein deficiencies such as were observed in this group of cases cannot be corrected entirely or even chiefly by oral feeding.

6. The most important therapeutic measure in hypoproteinemia of this degree proved to be the use of transfusion, in the form of either whole blood or of plasma. Each patient received an average of four transfusions, totaling 2,000 c.c. of blood. The transfusions were given repeatedly, at fairly close intervals, and in large quantities, since no other method results in a sustained rise in the serum protein concentration. We observed elevations of as much as 0.5 Gm. following a single transfusion of 500 c.c. of whole blood, but never observed maintenance of the improvement unless additional transfusions were given without undue delay (Fig. 2).

The clinical improvement which followed even small elevations of the serum protein level in these cases furnishes added proof that there is no "critical level" at which edema appears or disappears. Clinical observation suggests that when the vicious cycle which produces edema is interrupted by raising the plasma protein concentration, thus increasing the plasma colloid osmotic pressure, a polyuria is produced which usually continues until the water balance is restored and the edema has completely disappeared.

At the beginning of the treatment whole blood is more desirable than plasma, because of the anemia frequently associated with hypoproteinemia. After the anemia has been corrected, the use of plasma is more desirable, for several reasons besides the obvious one that there is no point to overloading the circulation with red blood cells which are not needed. Plasma can be stored indefinitely without deterioration, and therefore is always available. It can be used without typing. It causes a minimum reaction. Finally, a given amount of plasma contains a much greater quantity of protein than does the same amount of whole blood; it has been estimated that 500 c.c. of plasma contains about 40 Gm. of protein, as compared with only 18 Gm. for the same amount of whole blood.

Cantarow¹⁸ and Weech and his associates¹⁹ do not believe that it is practicable to correct the protein deficit in patients with edema due to hypoproteinemia by the use of whole blood or of plasma or serum transfusion because these measures produce only a relatively slight rise in the serum albumin concentration. This has not been our experience. The elevation is frequently much greater than one would theoretically expect, and the good results can possibly be explained by the stimulating effect of the administration of protein on the endogenous mechanism for protein regeneration and synthesis. We have observed a similar stimulating effect when blood transfusions are administered in anemia or when hypertonic dextrose solutions are used for the relief of edema in the toxemias of pregnancy.

7. Human ascitic fluid, advocated by Davis and White²⁰ as a substitute for blood or plasma, was used in one case in this series, but the reaction was so severe that we did not feel justified in using this method again. We did not employ any of the various other measures suggested to increase serum protein concentration, including concentrated plasma²¹ or serum²² (both of which would undoubtedly be of value), essential amino acid mixtures,²³ or gum acacia.²⁴

Results.—The average length of treatment in these eight cases was seventeen days. During this period, the average weight loss was 8.5 kg., and the range 7.4 to 19 kg. All the patients were free from pitting edema prior to delivery.

The average serum protein at delivery was 6.8 Gm. per cent, as compared with 4.20 Gm. per cent when the patients were admitted; the range at delivery was 5.8 to 7.5 Gm. per cent, as compared with 3.0 to 5.4 Gm. per cent on admission. The average hemoglobin at delivery was 10.2 Gm. per cent, as compared with 7.3 Gm. per cent on admission, and the average red blood cell count was 3,650,000 per c. mm. at delivery, as compared with 2,660,000 on admission.

There were no maternal or fetal deaths. The average weight of the children was 3.6 kg. (7.92 pounds). None of them had demonstrable edema or exhibited any other abnormality, and their serum protein and blood values were within normal limits.

SUMMARY AND CONCLUSIONS

1. Nutritional edema is due to a protein deficit caused by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. It is frequently associated with anemia. Contributory factors include hot weather, overwork, the excessive ingestion of salt and water, and the dependent position.

2. In pregnancy, the protein demands of the organism are increased far above normal, and cannot be met by a patient suffering from a chronically lowered protein reserve. A state of hypoproteinemia therefore results, and is manifested clinically as so-called nutritional edema. The time of the appearance of the edema, its degree and site, and its final disappearance are dependent on a number of other factors, of which anemia is probably the most important.

3. The etiology of nutritional edema determines the corrective therapy, which includes, in severe cases, general measures, such as bed rest, dextrose infusions, and the parenteral administration of vitamins B₁ and C; and specific measures, such as a high protein diet and the replacement of the serum proteins by transfusions of plasma or whole blood. If anemia is present, its correction is of great importance, but will be inadequate for the relief of the edema until the associated hypoproteinemia is also corrected.

4. This paper is based on a detailed study of eight patients in the last trimester of pregnancy, all of whom exhibited marked nutritional edema associated with hypoproteinemia and anemia. They were selected, by very strict criteria, from a group of approximately 500 pregnant patients with edema of various origins.

5. These eight patients, as well as 100 other pregnant patients studied from the standpoint of dietary intake, all revealed very marked protein, iron, and vitamin deficiencies. It would, therefore, seem that adequate prenatal care should include a careful dietary survey, with particular emphasis on these elements of the diet, and the prompt correction early in pregnancy of any dietary deficiency. Since impairment of the digestion, with associated impairment of absorption and utilization

of the dietary intake, is common in pregnancy, due allowance should be made for these losses in estimating the nutritional intake. Various diseases, infections, and infestations which cause rapid protein deficits should also be taken into consideration, as should an associated anemia.

6. Pregnant women should ingest a diet adequate in protein. The protein should be in a readily assimilable form, should be from animal as well as from cereal and vegetable sources, and should contain the necessary amino acids.

7. Incipient and mild cases of edema due to hypoproteinemia, if recognized promptly, usually respond satisfactorily to correction by an intensive use of the dietary measures suggested. The diet, in addition to being high in protein content, should also be high in carbohydrates, because of their caloric value, their protein-sparing action, and their beneficial effect on the liver. The restriction of sodium is advisable, and bed rest is helpful.

We wish to express our appreciation to Dr. William J. Dieckmann of the Chicago Lying-in Hospital for many helpful suggestions during the course of this study.

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SYPHILIS IN OBSTETRICS*

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OBSTETRIC syphilis has been so thoroughly studied and widely discussed that many phases of the problem can be considered settled for all practical purposes. There are, however, some particulars upon which there is no general agreement, and it is the purpose of this communication to analyze University Hospital Obstetric Service data which bear upon certain of these controversial issues.

GENERAL DATA

There were 400 women among approximately 11,000 admitted between Jan. 1, 1926, and Dec. 31, 1938, who were definitely syphilitic or who were strongly suspected of having the disease, and were therefore included in the analysis, an incidence of 3.6 per cent. One hundred and forty-four women, 36.0 per cent, were primigravidas, while 256 had been pregnant previously. Among the latter, 67 had been delivered in the Hospital on one or more previous occasions, and 55 were known to have been syphilitic at the time of the previous admission. The data, consequently, concern 345 individuals. The age range was from 14 to 43 years, with the median at 23 years. Three hundred and fifty-nine patients were white, 35 colored, and 6 Mexican. The latter two groups showed an incidence of syphilis from four to six times that of the white women.

TABLE I. OBSTETRIC SYPHILIS—GENERAL DATA

University Hospital (S. U. I.)—Jan. 1, 1926, to Dec. 31, 1938

Individual patients admitted		approximately 11,000	
Patients with syphilis		400	
Incidence	3.6+%		
Individual patients delivered		10,086	
Patients with syphilis		366	
Incidence	3.6 %		
Primigravidas	144	Single	92
Multigravidas	256	Separated	18
White	359	Divorced	13
Colored	35	Widowed	3
Mexican	6	Probably illegitimate	126
		Married	274

*Presented at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

SOCIAL DATA

Ninety-two, 23 per cent, of the syphilitic women were "single" as contrasted with an incidence of 14 per cent of single women among the total admissions. Moreover, 18 other patients were "separated," 13 "divorced," and three "widowed," and probably pregnant illegitimately, thus bringing the total of probable illegitimate pregnancies to 126, or 31.5 per cent.

TABLE II. 400 SYPHILITIC PATIENTS AMONG 11,000 PREGNANT WOMEN OBSERVED BETWEEN JAN. 1, 1926, AND DEC. 31, 1938

Discharged undelivered (outcome unknown)	32
Admitted with live baby shortly after delivery	2
Died in hospital undelivered	2
Delivered in hospital	364
Total	400
Incidence of syphilis, 3.6+ per cent	

Two hundred and one (50.3 per cent) of the 400 syphilitic women resided in urban centers (more than 10,000 population), which had only 30.4 per cent of the state population according to the 1940 census.

Three hundred and seventy-five patients were indigent, and 9 were "cost" patients. There were no syphilitic private patients, although this group represented 3.7 per cent of the total admissions.

CLINICAL DATA

The diagnosis of syphilis was made on the basis of positive serologic reactions (277 cases), or upon suggestive physical findings and definite history of infection (123 cases), including 54 doubtfully positive and 69 negative blood serologic reactions. In many instances the diagnosis had been made during a previous hospital admission. More than three-quarters of the women (305) had "latent" syphilis, while 13 had congenital, 27 early, and 15 late syphilis. In the 11 instances where the stage of the disease was not stated, it may fairly be assumed to have been latent.

FATE OF THE FETUSES

Exclusion of the 32 women who were discharged undelivered and of the two who died in the Hospital before parturition leaves 366 pregnancies terminated under observation. There were 5 sets of twins, which brought the total of observed fetuses to 371. Among this group were 14 abortions and 27 stillbirths, a total antepartum loss of 41, or 11.1 per cent. Three hundred and thirty children were born alive, but 14 (4.2 per cent) died during the neonatal period. The uncorrected fetal salvage, including children discharged alive and those transferred to the pediatric service, was 85.2 per cent. Exclusion of the 14 abortions raises the figure to 88.5 per cent.

TABLE III. 366 DELIVERED SYPHILITIC WOMEN, 5 SETS OF TWINS—371 FETUSES

Abortions (under 1,500 Gm.)		14
Spontaneous	11	
Criminal	2	
Therapeutic	1	
Premature (1,500 to 2,499 Gm.)		46
Discharged alive	22	
Stillborn	16	
Died in neonatal period	8	
Full-term (2,500 Gm. and above)		311
Discharged alive	294	
Stillborn	11	
Died in neonatal period	6	
Total		371
Total uncorrected fetal salvage, 85.2 per cent		
Fetal salvage excluding 14 abortions, 88.5 per cent		

The time when syphilis was contracted in relation to the pregnancy under consideration was known in 197 cases. The fetal salvage is greatest (89.4 per cent) when the original infection antedated the gestation but the small number of cases in the "at conception" and "after conception" groups makes the fetal mortalities hardly significant (Table IV).

TABLE IV. FATE OF FETUSES (371) IN RELATION TO TIME OF MATERNAL INFECTION

FATE OF FETUS	BEFORE CONCEPTION		AT CONCEPTION		AFTER CONCEPTION		NOT KNOWN	
Abortion	1		1		2		10	
Stillbirth	12		1		2		12	
Neonatal death	5		0		1		8	
Discharged alive	145		9		18		144	
Total	163		11		23		174	
	NO.	%	NO.	%	NO.	%	NO.	%
Abortions and premature births	18	11.0	2	18.2	6	26.1	34	19.5
Full-term births	145		9		17		140	
Discharged alive	145	89.4	9	81.8	18	78.3	144	82.8

Consistent with this evidence that time tends to attenuate the effect of maternal syphilis upon the children of an infected woman is the observation (Table V) that the highest fetal salvage occurred in the "latent" group and the lowest in those with early syphilis.

TABLE V. FATE OF FETUSES (371) IN RELATION TO STAGE OF MATERNAL SYPHILIS

FATE OF FETUS	CONGENITAL	ACQUIRED						NOT KNOWN		
		EARLY		LATENT		LATE				
Abortion	0	3		10		1		0		
Stillbirth	2	2		20		2		1		
Neonatal death	0	1		13		0		0		
Discharged alive	11	21		262		12		10		
Total	13	27		305		15		11		
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Abortions and pre-mature births	1	7.7	7	25.9	48	15.7	3	20.0	1	9.1
Full-term births	12		20		257		12		10	
Discharged alive	11	84.6	21	77.8	262	85.9	12	80.0	10	90.9

TABLE VI. FATE OF FETUSES (371) IN RELATION TO TIME OF MATERNAL TREATMENT

FATE OF FETUS	NOT TREATED BEFORE OR DUR- ING PREGNANCY	TREATED BEFORE BUT NOT DUR- ING PREGNANCY	TREATED DURING BUT NOT BEFORE PREGNANCY	TREATED BOTH BEFORE AND DURING PREG- NANCY
Abortion	8	1	5	0
Stillbirth	7	5	12	3
Neonatal death	9	1	1	3
Discharged alive	54	32	144	86
Total	78	39	162	92
	NO. %	NO. %	NO. %	NO. %
Abortions and pre- mature births	22 28.2	10 25.6	24 14.8	4 4.3
Full-term births	56	29	138	88
Discharged alive	54 69.2	32 82.1	144 88.9	86 93.5

The most potent factor favoring fetal survival is antisyphilitic therapy during the pregnancy. Table VI shows that the fetal risk is five times greater when no treatment has been given than when therapy has been offered before and during pregnancy. Evidently treatment before conception, excepting only the instances in which the syphilis has been serologically cured, offers little protection to the child in a succeeding gestation. Among the 66 women with seronegative syphilis, the fetal survival rate was 89.4 per cent, or, excluding two early abortions, 92.2 per cent. Among the four stillborn children and the one who died in the neonatal period, only one, a premature stillbirth, showed any post-mortem evidence of syphilis.

Abortion has been defined as the expulsion of a fetus weighing less than 1,500 Gm. and therefore generally previable. Using this criterion, there were 14 abortions, 3.8 per cent. In 9 instances, the fetus weighed more than 500 Gm., and in 6 cases more than 1,000 Gm. Only three of the 9 fetuses were subjected to autopsy, but they all showed lesions of congenital infection, and it is reasonable to assume that the others were infected except in one case where placenta previa was present and necessitated therapeutic measures which may have proved fatal to the fetus. Among the five early abortions there was one therapeutic intervention for pulmonary tuberculosis, two incomplete eriminal miscarriages, and two spontaneous abortions at ten and sixteen weeks, respectively. No autopsies were performed but it seems doubtful whether the interruption of the pregnancy could in any case be attributed to the maternal infection.

Stillbirths occurred in 27 cases, 16 times in the premature classification (1,500 to 2,499 Gm.) and 11 times with children in the term group (over 2,500 Gm.). Autopsies were performed in 25 cases with a pathologic diagnosis of congenital syphilis in 7, and with spirochetes demonstrable in only 3.

Fourteen children died in the neonatal period, and 12 were subjected to post-mortem study, with 6 deaths attributed to congenital syphilis, although the spirochetes were demonstrated only in 3.

It would then seem reasonable to attribute 8 abortions, 7 stillbirths, and 6 neonatal deaths directly to the maternal infection, and to view the lethal effect of the syphilis with some scepticism in the remaining 34 fetal fatalities. This, however, leaves such a high fetal death rate (34 out of 371), unexplained by delivery complications or by other recognized factors, that a majority of them may be attributed to the direct or indirect effect of the maternal syphilis.

LIVING CHILDREN

Three hundred and sixteen children (85.2 per cent) were discharged alive or transferred (30) to the pediatric service more than ten days after birth. In the latter group there were 5 premature and 25 full-term children; 10 were proved to be syphilitic and 17 nonsyphilitic, with the diagnosis undetermined in three. Five of the entire group died while under treatment, but death was attributed to syphilis in only one, who is not considered further in this study. The other 4 deaths were attributed as follows: erysipelas one, congenital cardiac disease one, and prematurity two.

The diagnosis of congenital syphilis in newborn children is admittedly difficult in spite of the various tests which have been introduced to facilitate differentiation and to hasten the inauguration of proper intensive therapy when indicated. None of the procedures commonly used (cord blood or vein blood serologic tests, histologic examination of the placenta, and x-ray films of the long bones) has proved reliable; errors in both directions are common, and even the usually accepted physical signs of syphilis in the first weeks of life may prove misleading. On the other hand, complete reliance can evidently be placed upon blood serologic tests performed at the age of two or three months. Consequently, the syphilitic status of the liveborn children in this series was considered only when this evidence was available in later pediatric records or from other sources.

By reason of the difficulties inherent in the admission of the patients from the entire state of Iowa, it has been possible to follow only 118 children sufficiently long to determine whether or not they should be considered congenital syphilitics, and the following discussion will involve only this group. It is unfortunate that there is such a large group with "undetermined status" and it is futile to discuss them, although it would not be unreasonable to assume that the incidence of congenital infection would closely parallel that in the thoroughly studied series.

The status of the living children in terms of the type of maternal syphilis (Table VII) shows nothing unusual except that one child of

TABLE VII. STATUS OF LIVING CHILDREN IN RELATION TO TYPE OF MATERNAL SYPHILIS

TYPE OF MATERNAL SYPHILIS	CHILDREN BORN ALIVE	SYPHILITIC STATUS		
		SYPHILITIC	NONSYPHILITIC	UNDETERMINED
Congenital	11	1	2	8
Acquired, early	21	5	5	11
Acquired, late	12	0	4	8
Acquired, latent	262	31	69	162
No data	10	0	1	9

The syphilitic status was considered "undetermined" when there were no clinical evidences of infection before discharge, and when no follow-up examination and later serologic study were possible.

Undoubtedly many of the children in this group were syphilitic.

eleven born alive to congenitally syphilitic mothers itself had congenital syphilis. It is commonly accepted that third generation offspring do not acquire the disease unless the mother has an acquired syphilis in addition to the congenital infection.

This particular woman had had one previous child, who showed no evidence of syphilis. She had been treated adequately before the second pregnancy as well as during the entire gestation period. However, her vein blood was still positive and the second child was finally diagnosed as being syphilitic, although there were no physical signs or positive laboratory findings in the neonatal period. The patient's husband had an old, acquired syphilis, a fact which suggests the transmissibility of the maternal infection by way of the imposition of acquired syphilis upon the congenital infection. It was to have been expected that early syphilis in the mother would endanger the child more than a late or latent infection.

The presence of negative maternal blood serologic tests does not assure an uninfected child; in two instances such mothers gave birth to syphilitic infants.

Both the cord blood and neonatal vein blood serologic tests proved unreliable, more often by indicating that a child had congenital syphilis when further study showed it to be uninfected. This situation developed in connection with cord blood studies on 29 of 45 proved non-syphilitic children, whose cord blood was studied, and in 19 of the 35 where vein blood was tested. Something more than one-half of the nonsyphilitic children would have been incorrectly diagnosed on the basis of these tests. It is also of interest that 5 of the congenitally syphilitic children had serologically negative cord blood and one showed a negative vein blood.

Other tests proved equally unreliable. Enlargement of the placenta to more than one-fourth of the child's birth weight was almost as common in the nonsyphilitic as in the syphilitic group, while the histologic changes supposedly characteristic of syphilis were found with 6 non-syphilitic children as against one syphilitic child.

TABLE VIII. SEROLOGIC FINDINGS IN LIVING CHILDREN KNOWN TO BE DEFINITELY SYPHILITIC OR NONSYPHILITIC

NATURE AND RESULT OF TEST	SYPHILITIC (37)			NONSYPHILITIC (81)		
	PREM.	TERM	TOTAL	PREM.	TERM	TOTAL
Maternal vein blood:						
Neg.	0	2	2	1	4	5
Doubt.	0	1	1	0	10	10
Pos.	5	29	34	5	61	66
Babies' cord blood:						
Neg.	0	5	5	1	11	12
Doubt.	0	1	1	1	3	4
Pos.	1	15	16	1	28	29
N.D.*	4	11	15	3	33	36
Babies' vein blood†:						
Neg.	0	1	1	2	9	11
Doubt.	0	0	0	1	4	5
Pos.	4	13	17	0	19	19
N.D.	1	18	19	3	43	46

*N. D., No data; not determined.

†During first few days of life (neonatal period).

TABLE IX. OTHER FINDINGS IN LIVING CHILDREN KNOWN TO BE DEFINITELY SYPHILITIC OR NONSYPHILITIC

NATURE AND RESULT OF TEST	SYPHILITIC (37)			NONSYPHILITIC (81)		
	PREM.	TERM	TOTAL	PREM.	TERM	TOTAL
Placental weight:						
More than $\frac{1}{4}$	1	3	4	1	5	6
Less than $\frac{1}{4}$	4	29	33	5	70	75
Placenta:						
Histologic changes	0	1	1	1	5	6
Normal histology	1	9	10	3	34	37
N.D.	4	22	26	2	36	38
X-Ray, long bones:						
Neg.	2	12	14	4	40	44
Doubt.	0	3	3	1	11	12
Pos.	1	6	7	0	4*	4
N.D.	2	11	13	1	20	21

Only 6 syphilitic babies showed clinical signs of syphilis in the neonatal period. Two others had "snuffles" and one an enlarged liver, all later shown to be non-syphilitic.

*Considered nonsyphilitic because of persistently negative serologic reactions.

X-ray examination of the long bones showed so many errors in both directions as to be practically useless; four nonsyphilitic children were interpreted as being positive, whereas 14 syphilitic children showed no long bone changes.

Only 6 of the 37 syphilitic children showed clinical signs of syphilis, —snuffles, skin lesions, and visceral enlargement; while two others with snuffles and one with an enlarged liver were later known to be uninfected.

Assuming the specificity of the various serologic tests for syphilis at the age of two to three months, as has been done here, it is obviously impossible to make an accurate diagnosis on a newborn child by any of the methods now available.

Whether or not it is justifiable to offer antisyphilitic therapy before a definite diagnosis is possible must continue debatable although probably little harm would ensue provided the therapy is not too energetic.

FATE OF THE MOTHER

There were four deaths among the 368 women cared for in the Hospital, and in each instance the fatality was directly attributable to antisyphilitic therapy, being due to arsenical encephalitis. Three of these cases have been reported previously, while the fourth occurred in 1937. In each instance, the fatal neurologic manifestations appeared after 2 to 6 neoarsphenamine injections of not more than 0.4 Gm., and death occurred in 24 to 36 hours. In three instances, the cause of death was confirmed at necropsy, while in the fourth the clinical picture was quite unequivocal.

In addition to these fatal reactions, there were 27 of less severity, as shown in Table X, among the 254 women treated in the hospital, a re-

TABLE X. TREATMENT REACTIONS AMONG 254 WOMEN TREATED DURING PREGNANCY

	NO.	PER CENT
Arsenical dermatitis	9	3.5
Local inflammatory reaction	8	3.1
Transient fever	5	2.0
Transient albuminuria	4	1.6
Arsenical encephalitis	4*	1.6
Arsenical hepatitis	1	0.4
Total	31	12.2
Treatment mortality		1.6%

*All four patients who developed arsenical encephalitis died, the only deaths in the series.

action incidence of 12.2 per cent. The fatality rate among the treated patients was 1.6 per cent, while other severe reactions (dermatitis and hepatitis) were present in an additional 3.9 per cent. Since the end of the period included in this survey, an additional death evidently due to arsenical poisoning has been observed. This patient, a primigravida, aged 15 years, received 10 doses of 0.3 Gm. arsphenamine over a period of twenty-one days. About halfway through the series smallpox vaccination was done and resulted in a take with several areas of secondary inoculation on the face, vulva, and breast. A few hours after the tenth arsphenamine injection the patient had a chill and then started in labor. She was delivered spontaneously the following day and died eighteen hours later. During the last two days of life the leucocyte count fell from 13,400 to 600 with no granulocytes. Autopsy showed acute pulmonary edema and lobular pneumonia, with blood and marrow evidence of agranulocytosis.

Experiences of this character appear to be unusual on the basis of reports in the literature, although there is an occasional suggestion that arsenical therapy may not be tolerated so well in pregnancy as in the

male and in nonpregnant women. There is no plausible explanation for this high percentage of fetal reactions, since the doses have not exceeded those commonly recommended and the treatment intervals have not been too short.

SUMMARY

Syphilis is an obstetric problem of considerable significance among patients in the lower economic groups, even in a predominately rural state such as Iowa, where most of the people are native born whites.

The fate of the offspring of syphilitic women appears to depend less upon the duration of the infection at the time of conception and previous antisyphilitic therapy than upon the character and extent of treatment during pregnancy. The best results are obtained when treatment during pregnancy follows antekonceptional therapy.

None of the diagnostic measures available makes possible the determination of the syphilitic status of the child of a syphilitic woman during the neonatal period. Standard serologic tests are practically pathognomonic at the age of two or three months and are alone to be depended upon.

The syphilitic pregnant woman appears especially likely to develop treatment reactions to the arsenical antisyphilitic drugs, which should, therefore, be used with caution.

DISCUSSION

DR. JAMES R. REINBERGER, MEMPHIS, TENN.—While sufficient attention has been devoted to the care of the unborn, too little interest has been directed toward ill effects of syphilitic therapy. Dr. Plass's presentation of such ill effects in his article, "Hemorrhagic Encephalitis Following Intravenous Arsphenamine," centered my attention upon this subject in 1935. Since that time three recognized deaths from such causes have occurred on the obstetric service of the John Gaston Hospital of the University of Tennessee, five additional cases with severe reaction have also been recorded.

In an effort to compare the frequency of fatal accidents among all patients receiving neoarsphenamine in the John Gaston Hospital with the incidence of deaths from this drug during pregnancy, I found that there were 15 deaths in the 91,441 patients admitted to the hospital during the years 1935 through 1940, against 3 deaths in 13,316 obstetric patients admitted during these same years. In other words about one patient died in 4,453 in the pregnant; and, 6,096 in the non-pregnant. This would indicate that there is not more susceptibility in the pregnant patient. A review of such deaths showed very definitely, however, that the minor reactions to arsenic in all of its compounds are too often overlooked until a major catastrophe results from continued treatment.

The end results in the treatment of the syphilitic mother or in the newborn baby were in general the same as those presented by Dr. Plass. In a series of 1,000 consecutive cases of syphilis in pregnancy, reported by Reinberger and Toombs in *The Southern Medical Journal* in 1933, it was found that, despite treatment, there were 35 per cent of syphilitic tragedies including abortion, premature labor, still-born and infected newborns. This study stressed moreover:

1. that antisyphilitic treatment is indicated in each case;
2. that the earlier treatment is begun, the more unlikely syphilitic tragedies;

3. that pregnancy does not alter the Wassermann reaction;
 4. that serologic more often than clinical evidence is present in the treated infected newborn infant;
 5. that antisyphilitic treatment is indicated in every pregnant woman ever known to have syphilis, irrespective of her present serologic or clinical findings; and
 6. that despite most intensive therapy syphilitic tragedies must be expected in some cases.
-

A REVIEW OF SEVENTY-FIVE CASES OF ECLAMPSIA*

WITH PARTICULAR REFERENCE TO LATE CARDIOVASCULAR RENAL EFFECTS

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INABILITY to determine a specific cause for the toxemias of pregnancy has resulted in an attempt to explain them in relation to known cardiovascular renal diseases, such as hypertensive vascular disease, vascular nephritis, and acute or chronic glomerulonephritis. This trend is obvious in recent years in the writings of both obstetricians and internists who have become interested in these special problems of obstetrics. Many authors have held the view that an unduly high proportion of women who have had toxemia during pregnancy will later in life be found to have hypertensive vascular or renal disease.

This paper represents a preliminary study of observations made on seventy-five patients who were diagnosed as having eclampsia in the Vanderbilt University Hospital during the past fourteen years. An attempt has been made to determine, where later information was obtainable, the presence or absence of hypertension, vascular or renal disease, and the present discussion is chiefly concerned with this phase of the problem. The diagnosis in the cases under discussion has been made on the basis of the development of hypertension and convulsions in the last trimester of pregnancy where there was no evidence of chronic renal disease.

Of the 75 cases, 49 were primiparas and 26 were multiparas. This ratio of a little less than 2 to 1 is lower than is given in other reports.^{1, 7} The ages of these patients were from fifteen to forty-four years with 86 per cent of the primiparas and 27 per cent of the multiparas below twenty-five years of age.

Of the 26 cases of eclampsia among the multiparas, 11 occurred during the second and third pregnancies. Two occurred in women who had been pregnant ten or more times.

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MATERNAL MORTALITY

The immediate maternal mortality was 13.3 per cent. Ten of these patients died in the hospital. One of them died of pulmonary emboli from a pelvic thrombophlebitis during post-partum convalescence. It is pertinent that none of these patients had received any prenatal care, and they were either moribund on admission to the hospital or went into profound shock following delivery. Those who were moribund had all the symptoms and signs of the severest type of eclampsia, such as coma, 10 or more convulsions, extremely high blood pressure, rapid pulse, and elevation of temperature. These facts support the viewpoint of many investigators that the earlier the disease is treated, the more favorable the prognosis.

Three of the patients who died had spontaneous deliveries and two were delivered by low forceps. Three of the 10 patients died undelivered. Two of the deaths followed cesarean sections. There were only 5 cesarean sections done among the 75 cases. This number is too small to justify any conclusion as to the advisability of using this treatment in eclampsia. However, it is generally agreed among authors that the surgical approach in the treatment of eclampsia is associated with a maternal mortality of from 23 to 48 per cent.^{2, 3}

Of the 65 individuals discharged from the hospital only one is known to have died. This patient died at fifty years of age, ten years after an attack of eclampsia, from cardiac failure and pulmonary atelectasis following an operation for repair of an incarcerated ventral hernia in the site of a scar resulting from a cesarean section. An autopsy revealed generalized arteriosclerosis with benign nephrosclerosis, cardiac hypertrophy, and congestive failure. There was no evidence of glomerulonephritis.

OUTCOME IN THE FETUS

The gross fetal mortality for the group was 26.7 per cent. Included in the 20 deaths were 3 babies which were undelivered and 2 which died during the first week of life. There was no apparent relationship between the fetal mortality and the number of convulsions.

It is interesting to note that there were 3 sets of twins, making an incidence of 1 in 25 deliveries. This is about three times the average and follows the general conception that late toxemias are found more frequently associated with multiple pregnancy.⁴⁻⁷

RESULTS OF FOLLOW-UP

Follow-up observations were made on 42 of the 75 cases of eclampsia studied. It was decided, however, that no observations made less than six months post partum would be included in the following tabulations since most of these occurred between the fourth and eighth week post partum. The effect of this decision was to exclude 12 patients from

consideration. There remained 30 patients on whom 55 observations were made at varying lengths of time since the pregnancy in which eclampsia occurred. These 55 observations are shown in Table I.

TABLE I. LENGTHS OF FOLLOW-UP AFTER THE PREGNANCY IN WHICH THE ECLAMPSIA OCCURRED

YEARS SINCE PREGNANCY	NO. OF OBSERVATIONS
6 months to 1 year	11
1- 2 years	11
2- 3 years	6
3- 4 years	4
4- 5 years	2
5- 6 years	8
6- 7 years	3
7- 8 years	3
8- 9 years	1
9-10 years	—
10-11 years	3
11-12 years	—
12-13 years	—
13-14 years	3
Total	55

Table II shows the number of follow-up observations made in each age group and the number with systolic pressures of 140 mm. or more in the respective age groups. Thus, out of the 55 observations made at varying ages following the pregnancy in which eclampsia occurred, 11 were found to have a systolic pressure of at least 140 mm. It is difficult to obtain a series of observations to use as controls which are not selected in one form or another. Comparison is made in Table II with observations made by Saller⁸ on women attending the outpatient clinic in Kiel, Germany; with Wetherby's⁹ data for women in the Minneapolis outpatient clinic; with blood pressure readings made during a nutritional study¹⁰ on a sample of the women living in Wilson County, Tennessee; and with observations before the third trimester on a group of presumably normal obstetric patients who returned to the outpatient service of Vanderbilt University Hospital with subsequent pregnancies.

For each of the four control groups, the percentage of observations showing a systolic pressure of 140 mm. or more was computed for each age group. These percentages were then applied to the number of observations in that age group of women who had had eclampsia. This yielded the number of observations which would be expected to have a systolic pressure of 140 mm. or more in each age group if the incidence of hypertension in the eclamptic group were the same as in each of the control groups. These expected values and their totals for all ages are shown in Table II.

Thus it is seen that if the incidence of hypertension in the post-eclamptic group were the same as found in Saller's and Wetherby's outpatient clinics 10 and 9 cases of hypertension, respectively, would be expected for the group as a whole. The number observed (11) was

TABLE II. COMPARISON OF OBSERVED AND EXPECTED NUMBER OF WOMEN AT CERTAIN AGES WITH SYSTOLIC PRESSURES OF 140 MM. OR MORE

AGE	OBSERVED DATA		NUMBER OF CASES EXPECTED IF THE INCIDENCE WERE THE SAME AS IN			
	TOTAL OBSERVATIONS	OBSERVATIONS 140 MM. OR MORE	SALLER'S OUTPT. CLINIC	WETHERBY'S OUTPT. CLINIC	WILSON CO. POPULATION	WOMEN WITH NORMAL PREG.
15-19	2	—	—	—	—	—
20-24	16	1	2	} * 2	—	} * 1
25-29	12	—	2		1	
30-34	9	3	1	} * 3	2	} * 1
35-39	9	1	2		2	
40-44	4	3	1	} * 3	1	
45-49	1	1	1		—	
50-54	2	2	1	1	1	
Total	55	11	10	9	7	
Number of cases in control group			1,270	2,695	224	170

*Ten-year age period.

practically the same. It must be remembered, however, that there is a tendency for observations in outpatient clinics to be selected for relatively high blood pressures.

When comparison is made with the Wilson County population group it is seen that the incidence of hypertension among the post-eclamptics is slightly higher than would be expected; the comparable figures being 11 for the post-eclamptic group and 7 for the sample of Wilson County population. The difference, however, might very well arise solely as a matter of chance, and further observations are needed before one may say that the incidence of subsequent hypertension is greater among women who have had eclampsia than among the population in general.

No observations were made above the age of thirty-nine in the group of women with normal pregnancies. Five observations of 140 mm. systolic pressure or higher were observed in the comparable age groups, whereas only two would be expected. Here, however, the selection present in the control group is in the direction of low blood pressures. These findings are presented merely to obtain some idea of the relative position of readings on a group of women who have had eclampsia when compared with four groups such as those indicated.

Comparison of the incidence of diastolic pressures of 90 mm. or more between the post-eclamptic and the control groups is shown in Table III. In general, the findings are the same as were noted for systolic pressures.

Urine examination at the time of follow-up showed at least a two-plus proteinuria in only 2 of the 55 observations.

In addition to information obtained at the time of the follow-up examination on the above 30 patients, it was possible to contact 9 other patients by letter with regard to their subsequent pregnancies. Among these 39 patients, a total of 32 pregnancies were reported following the pregnancy in which eclampsia occurred. There was no recurrence of eclampsia in any of these later pregnancies.

TABLE III. COMPARISON OF OBSERVED AND EXPECTED NUMBER OF WOMEN AT CERTAIN AGES WITH DIASTOLIC PRESSURES OF 90 MM. OR MORE

AGE	OBSERVED DATA		NUMBER OF CASES EXPECTED IF THE INCIDENCE WERE THE SAME AS IN			
	TOTAL OBSERVATIONS	OBSERVATIONS 90 MM. OR MORE	SALLER'S OUTPT. CLINIC	WETHERBY'S OUTPT. CLINIC	WILSON CO. POPULATION	WOMEN WITH NORMAL PREG.
15-19	2	—	—	—	—	—
20-24	16	2	3	{ * 4	—	{ * 1
25-29	12	1	3		2	
30-34	9	2	2	{ * 4	1	{ * —
35-39	9	3	2		2	
40-44	4	3	1	{ * 2	1	{ * —
45-49	1	—	—		—	
50-54	2	1	1	1	1	—
Total	55	12	12	11	7	—
Number of cases in control group			1,261	2,695	224	170

*Ten-year age period.

DISCUSSION AND SUMMARY

In the last fourteen years 75 cases of eclampsia have been diagnosed in the Vanderbilt University Hospital. Forty-nine of these patients were primiparas and 26 were multiparas.

The immediate maternal mortality was 13.3 per cent. None of the patients who died had had any prenatal care, a fact tending to emphasize again the findings of other investigators that the earlier the disease is treated, the better the prognosis. Only one of the 65 individuals discharged from the hospital is known to have died. This individual was fifty years of age at the time of death, which occurred ten years after an attack of eclampsia.

In order to study the question of whether or not an unduly high proportion of women develop hypertension after having had an attack of eclampsia an attempt was made to follow up the patients studied. A total of 55 observations was made on 30 individuals. While the length of follow-up ranged from six months to thirteen years, half of the observations were made within three years. Because of the relatively small number of cases and because of the short length of follow-up, the present discussion should be considered a preliminary report.

The number of cases of hypertension which developed among the post-eclamptic patients was compared with observations made on the blood pressure of women attending outpatient clinics in Kiel, Germany, in Minneapolis, with observations made on a sample of the women living in Wilson County, Tennessee, and with readings before the third trimester on a group of women who returned to the obstetric outpatient service of the Vanderbilt University Hospital after having had a normal pregnancy.

In general, the evidence in this study does not indicate that individuals who have had attacks of eclampsia develop hypertension in any

undue proportion; however, further observations are required before any definite conclusion may be reached.

It should be pointed out that even if a high relationship is shown it does not necessarily mean an etiologic relationship. The very nature of eclampsia is such that one would suspect that its severe strain on the cardiovascular system might not only bring out a latent but even initiate hypertensive vascular disease.

Dieckmann and Brown⁴ have summarized the literature on this subject. They find an average incidence of 27 per cent hypertension and 19 per cent chronic nephritis subsequent to attacks of eclampsia. In making comparisons, recognition should be taken of the possible lack of conformity in making the diagnosis of hypertension and chronic nephritis. Not all authors make a distinction between hypertensive vascular disease, vascular nephritis, and glomerulonephritis. One should also take account of the length of time over which the patients have been followed.

Teel and Reid¹¹ reported that a follow-up examination of patients who had had eclampsia showed an incidence of hypertension among all cases of 27.5 per cent. After 7.6 years, however, in the group known to have had normal blood pressure and urine previous to the pregnancy with eclampsia, the incidence was only 10.3 per cent. They found a higher incidence of hypertension in the noneconvulsive, mild toxemias than in eclampsias, and stated that "the commonly held viewpoint that eclampsia frequently causes permanent and progressive vascular or renal damage is not substantiated by our data."

There were no cases of chronic glomerulonephritis in our follow-up group and in none of the 32 subsequent pregnancies was there any recurrence of eclampsia. This finding supports the view of Dieckmann that the incidence of recurrence is inconsiderable.

The solution of as complex a problem as eclampsia requires the integration of a large number of laboratory, clinical, and epidemiologic observations. Adequate controls will need to be established and follow-up will require a sufficiently long time to allow full observation of after-effects. It is hoped that it will be possible to continue the present study to fulfill these requirements.

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DISCUSSION

DR. C. RAYMOND MAYS, SHREVEPORT, LA.—We have an abundance of eclamptic material at Shreveport Charity Hospital. The patients come in great part from the surrounding countryside, and we, therefore, have little opportunity to observe their subsequent status. They are invariably without prenatal care and their previous vascular history is not often available. However, from returning patients, the few followed in the city welfare clinics, private cases, and frequent conferences with the pathologist and medical staff, we have formulated some ideas about the immediate and remote welfare of the eclamptic mother and her fetus.

The immediate mortality of the mother is augmented by her age, the degree and duration of hypertension, delay in time of treatment after the onset of the disease, the number of fits, pre-existing vascular or renal damage, and oversedation. We feel that we have sacrificed some cases in the past by rigid adherence to a nonoperative policy and have recently adopted the policy of cesarean delivery in fulminating cases, and in patients who become worse after twenty-four to forty-eight hours of medical treatment, especially if a tedious labor is in prospect.

The fetal mortality is increased by the same factors that augment maternal mortality plus prematurity and the lapse of more than forty-eight hours from the time of the onset of the eclampsia to the delivery.

As for the latent effects of eclampsia, a few will be found to have subsequent hypertension because of the pre-existence of pyelonephritis, polycystic kidneys, and glomerulonephritis. A larger number will have had pre-existing essential hypertension.

As for the hypertensive states acquired during the pregnancy, we recognize that they conform roughly to two types, one slowly progressive with little edema, little albuminuria and few symptoms, the other with rapidly mounting pressure, water retention, early symptoms, and a very labile blood pressure. Eclampsia is more common in the latter group, but the former not infrequently become suddenly worse and have unpredicted eclampsia. In either group, if the blood pressure was normal before pregnancy, we classify them as pre-eclampsia. They are regarded pathologically and possibly etiologically as eclampsia, though they are not manifestly such.

We feel that there is no reason to re-classify these obstetric diagnoses because of persistence of hypertension after the pregnancy. It is our opinion that both groups are made up of women who by heritage have the nervous, endocrine, and vascular background that makes them subject to development of vascular or vascular-renal disease. Without delving precariously into the etiology of pre-eclampsia, we surmise that pregnancy toxemia results from the liberation of angiotoxic or angiotonic materials by the kidney, placenta, or both, or, that pregnancy depresses the organism's ability to inactivate these materials. In any event, the development of toxemia is enhanced by pre-existing vasolability or latent hypertension.

The persistence of hypertension after all toxemias of pregnancy is at the rate of 40 or 50 per cent and after those having eclamptic convulsions is probably 15 or 20 per cent. In either of the above groups, the persistence of hypertension is determined by the pre-eclamptic course and not by the eclamptic outbreak itself. There are many factors in the prenatal course that predetermine the ultimate vascular status, such as age at the eclamptic attack and age at follow-up periods, complicating pyelonephritis, family history of hypertensive disease, etc., but the two most important factors seem to be the duration and height of the pre-existing blood pressure and the added assault of a subsequent toxemia. The added hypertension after the second toxemia is unrelated to the occurrence of convulsions and is in proportion to the duration and intensity of the toxemia and to the immeasurable underlying vascular lability.

I infer that the 32 pregnancies among the 9 patients having subsequent pregnancies in Dr. McClellan's series were not among those available for follow-up study, and that he does not know whether or not they had noneconvulsive hypertension with the succeeding pregnancy or hypertension after their subsequent pregnancies. Chesley and Somers' recent survey of the sequelae of eclamptic women at the Margaret Hague Maternity shows a relatively increased incidence of hypertension over Wetherby's and Saller's groups similar to that shown by Dr. McClellan's cases over the Wilson County control groups.

All in all, we feel that the future medical welfare of patients who have had eclampsia is not bad provided it was not preceded by prolonged hypertension, but that future pregnancy is fraught with danger of recurrence of toxemia that will result in permanent hypertension unless it is brought under prompt control by medical management or termination of the second toxie pregnancy. If the recurrent toxemia is severe or long standing, we perform puerperal sterilization on the patient. If the previous course is unknown and the present blood pressure is not severely elevated, the heart not enlarged, the urine well concentrated, the eye grounds relatively normal, we have her return at three months for further study. We see no reason to subject any hypertensive woman who already has two or three babies to the hazardous test of future pregnancy, notwithstanding the exceptional case that stands recurrent toxemia well.

Dr. McClellan's contribution indicates that the subsequent welfare of the eclamptic woman is not as bad as some of us had thought, but I do not think he intends to convey the idea that we are yet in a position to assume a cavalier attitude toward the future cardiovascular renal welfare of the eclamptic woman.

DR. R. E. ARNELL, NEW ORLEANS, LA.—Among the 24,205 obstetric admissions to the New Orleans Charity Hospital during the five-year period ending Jan. 1, 1941, there were 220 cases of eclampsia, an incidence of 0.90 per cent. In 4 of the patients with eclampsia, convulsions had been present in a previous pregnancy, a recurrence incidence of 1.8 per cent. From these gross statistics it would appear that a patient with a history of eclampsia is twice as likely to have eclampsia in a subsequent pregnancy as one whose obstetric history is normal.

In an attempt to determine the late effects of eclampsia and to evaluate the medical and obstetric future of these cases, 30 patients with a history of eclampsia, one to five years previously, were admitted to the hospital for study. Numerous examinations and tests were made in each instance, including complete physical examination, urinalysis, urea clearance, blood chemistry, vasomotor lability, eye grounds, electrocardiogram, and liver function. Except in one case all were normal. This patient exhibited an elevated blood pressure and apparently had an essential hypertension.

We are in agreement with the essayist that demonstrable cardiovascular renal effects following eclampsia are relatively rare. Furthermore, if they do occur, the patient may have had an encephalopathy due to hypertensive or renal disease as the basis for the convulsions rather than a specific eclampsia. We are of the opinion that this occurs not infrequently.

DR. E. L. KING, NEW ORLEANS, LA.—I believe we might estimate the amount of damage that has been done by the eclampsia if we could get a history of that patient for two or three years before the pregnancy that would tell whether there is any underlying factor that might induce the eclampsia. It is evident that pure 100 per cent eclampsia developing in a healthy patient very seldom leaves a permanent lesion.

Another question in this connection is what are we to tell patients regarding future pregnancy. I have known instances where patients who had eclampsia

have been warned never again to become pregnant. This is unnecessary, and keeps the patient in a state of worry for fear of possible pregnancy. I think, however, we should warn these patients not to become pregnant too soon, for it takes a long time to get over the damage.

I have one patient, treated a good many years ago in her first eclamptic attack, whom we warned to wait reasonable time before becoming pregnant again. She disregarded the warning and inside of four months she was again pregnant. She developed a mild attack of eclampsia within the year. After that she listened to reason and waited four or five years, and went through her third pregnancy successfully, and then after four or five years went through another. She has a hypertension of 240 to 245 systolic at present, so that she does have damage as the result of two attacks of eclampsia.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—We use the term eclampsia rather loosely. In a discussion like this we should not speak of eclampsia as being synonymous with toxemia, but rather we should consider eclampsia as being a specific type of toxemia, the chief characteristic of which is that it is a condition which does not exist prior to the particular pregnancy but develops during the pregnancy. The question is whether such a condition is likely to have late cardiovascular and renal sequelae. Of course it is reasonable to expect that other types of toxemia which antedate the pregnancy should persist after the pregnancy is terminated.

In the early Williams' textbooks, the opinion was expressed that an attack of eclampsia might cause an immunity. It seems to me that this earlier view is definitely challenged by the work of Peckham who found that a surprising number of eclamptic patients later on showed evidences of renal disease. My belief is that eclampsia is not as innocuous as far as late sequelae are concerned as we formerly thought it was.

DR. McCLELLAN (closing).—The statements of the patients who were contacted by letter are the only source of information we have regarding their condition. Their specific reference to the absence of recurrence of convulsions can be relied on, I am sure. This fact, along with our observations of patients seen in pregnancies subsequent to the one in which eclampsia occurred, I believe, makes the statement regarding recurrence of eclampsia reliable.

I quite agree that one should not tell these patients that they should never become pregnant again or that it will be all right to conceive again. They should be followed for a year with frequent blood pressure readings and urinalyses and then advised either against pregnancy or that they might again become pregnant in two or three years.

I would like to emphasize again the importance of differentiating hypertensive vascular disease, vascular nephritis, and glomerulonephritis. Reference was made to Peckham's series in which a certain percentage of post-eclamptics had chronic nephritis. The above differentiation was not made, and unless it is, the figures reported are misleading.

DIAPHRAGMATIC HERNIA IN THE NEWBORN INFANT*

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INTERFERENCE with the establishment of normal respiration in the newborn should evoke the interest of the obstetrician, even though the ultimate responsibility for care and treatment may properly belong in other divisions of medical practice. All entities causing newborn respiratory embarrassment are, therefore, obstetric problems.

Respiratory difficulties of central nervous system origin, such as from intracranial hemorrhage and from obstetric analgesics and anesthetics, have received much attention. Recently our attention has been called to respiratory difficulties which result from abnormalities in the chest cavities themselves. An example of this is the report, in 1939, by DeCosta describing and reviewing spontaneous pneumothorax in the newborn, emphasizing that early recognition and immediate treatment will save many of the infants so affected.

The recent occurrence of two cases of congenital diaphragmatic hernia in the newborn infant, precipitated a review of the subject. This condition was formerly considered to be extremely rare and until 1935 was thought to be unamenable to treatment. It is in reality not rare, and, furthermore, can be treated surgically with more than a 60 per cent recovery.

CASE 1.—The infant was a 3,400 gram female born at term after a labor of four and one-half hours. The mother was a primigravida, aged 28 years. There was no history of congenital defect in either parent. The infant breathed spontaneously and cried lustily. She was taken to breast five times the following day and nursed well each time. The baby's progress continued uneventfully until her fourth day of life, when, after a breast feeding, she became cyanotic. This lasted but a few minutes. Following the next feeding the cyanosis became so severe that oxygen was administered. The attending resident pediatricist reported the attack to be so severe that he thought the infant would die. Upright position and oxygen were continued. Examination showed that the heart was pushed to the right and no breath sounds were heard in the left chest. An x-ray revealed a left diaphragmatic hernia. On the ninth day, a laparotomy was performed. The entire small intestine and the spleen were in the left chest cavity. These viscera were replaced in the abdomen and the defect closed. She made an uneventful recovery and was discharged on the twenty-ninth day of life, twenty days postoperatively. The infant's development has continued normally.

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., October 2 to 4, 1941.

CASE 2.—A full-term male infant, weighing 2,800 Gm., was delivered by low forceps after rotation of the occiput from a posterior position to the anterior. Labor lasted but four hours. The mother was a

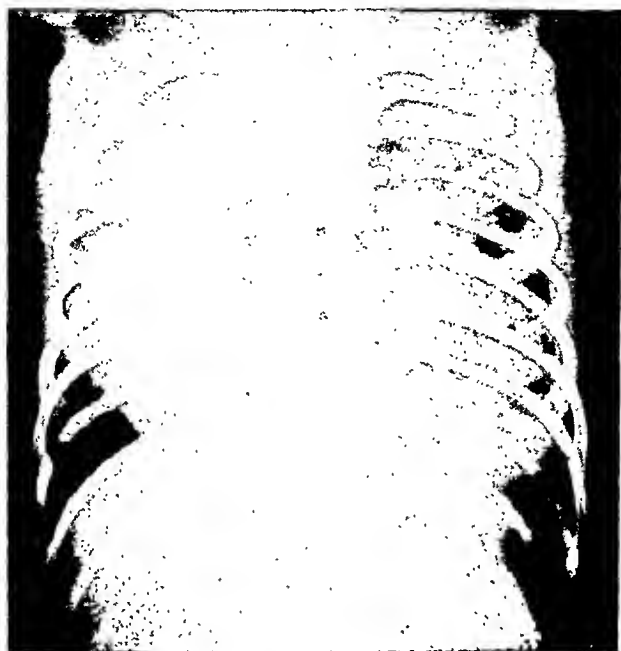


Fig. 1.—Case 1. X-ray film, taken preoperatively, showing left diaphragmatic hernia with intestinal tract in the left chest cavity, and the mediastinum displaced to right.



Fig. 2.—Case 1. Eleven days postoperative, showing diaphragm intact, mediastinum returning to center, and with the left lung partially expanded.

29-year-old primigravida. Both mother and father had a negative history for congenital defects. The child gave a single weak cry which was followed by cyanosis and labored grunting respirations. The larynx was visualized with a directoscope and the air passage proved to be clear. Oxygen was administered, which relieved the cyanosis somewhat.

Breath sounds were absent in the right chest and the mediastinum was found to be displaced to the left. An x-ray revealed a diaphragmatic hernia on the right side. The infant's condition became progressively



Fig. 3.—Case 1. Fifteenth postoperative day, showing further expansion of the left lung.

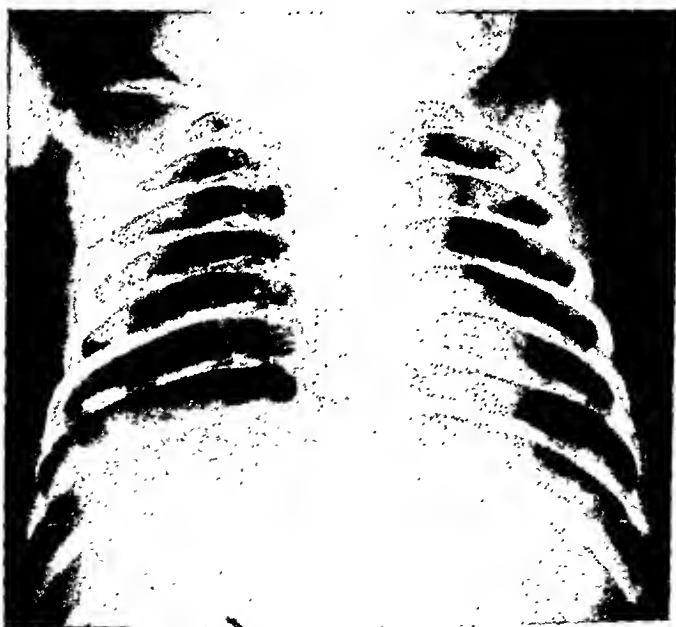


Fig. 4.—Case 1. One month postoperative. Complete cure.

worse. Approximately six hours after birth, the abdomen was opened through a right rectus incision. Nearly the entire gastrointestinal tract and about half of the liver was in the right chest cavity. These viscera

were replaced in the abdomen and the large defect was closed with interrupted chromic catgut sutures. The child died while the abdominal wall was being closed.

A review of the literature reveals a distinct change in thought regarding the incidence and surgical treatment of this condition.

Vannesson, in 1912, reported 34 cases in the newborn, all discovered at autopsy. He stated that the prognosis was grave and that no treatment had been devised.

In 1914, Broca described the condition accurately. He stated that nearly all cases were discovered at autopsy, and he gave the operative mortality as 90 per cent.

In Abt's text on *Pediatrics*, Richter made the statement that congenital large hernias, present from birth, offer little opportunity for surgical treatment.

In 1934, Tremolieres stated that the large congenital diaphragmatic hernias are not amenable to surgical treatment.

Griffith and Mitchell, in 1927, devoted but two paragraphs to the subject with the conclusion that the condition is rare. They stated that surgery is indicated only when obstruction occurs and that it is not likely to be of any avail.

Woolsey, in 1927, was one of the earlier writers to express a change in viewpoint. He collected 106 cases from the literature. In his entire group there was a 71 per cent mortality. It is of interest that he stated that had an early diagnosis been made and operation performed, this figure might have been markedly reduced.

Truesdale, in 1935, collected 303 cases in infants and children. Forty-four had been operated upon, 24 successfully and 20 with fatal termination, a mortality rate of 45.5 per cent. This is quite a different result than was described by the earlier writers.

Truesdale's own series of congenital diaphragmatic hernias totaled 10 cases, all of which he operated upon with but one death. One patient was operated upon three times for recurrences, so his operative mortality was only 7.7 per cent.

Truesdale strongly advocated that operation should be done in the early weeks or months of life.

Wyatt recently reported three patients operated upon in the immediate neonatal period, two of whom survived. His conclusion was that if we expect to reduce the mortality of congenital diaphragmatic hernia, the infants must be operated upon in the first hours or days of life.

INCIDENCE

In a series of 5,269 autopsies on stillbirths and infants up to one year of age, from the Department of Pathology at the University of Minnesota, there were 38 diaphragmatic hernias, or one in 139 autopsies in this age group.

The Chicago Lying-in Hospital has a series of 1,700 infants and fetuses born with malformations. Potter states that there were 70 diaphragmatic hernias in this group. It is of interest that 53 of these infants were liveborn and 17 stillborn. Ten of these 70 infants were

born at Lying-in Hospital. These ten were from a period covering 21,000 deliveries. During most of the years of this period about 95 per cent of the dead babies were autopsied. Consequently, one might assume that these ten are practically all that occurred among infants born at Lying-in Hospital during this time.

These two series indicate that this condition should not be considered a medical oddity.

Diagnosis.—The obstetrician's main concern is with symptoms and signs that occur immediately or in the first few hours after birth. Final diagnosis can be made with ease by x-ray. However, certain signs and symptoms are frequently present which make a clinical diagnosis possible. There is no interference with the mechanism which initiates respiratory attempts; consequently, these babies, in the absence of other abnormalities, will make their initial respiratory attempts normally and promptly. A characteristic single weak cry followed by cyanosis is described by Greenwald and Steiner. This is followed by convulsive attempts at respiration, bringing into play all of the auxiliary muscles. Displacement of the mediastinum away from the affected side with change in percussion note and absence of breath sounds is the rule. Occasionally, gurgling sounds can be auscultated over the thorax due to the presence of intestines in the chest cavity. Our second case presented this entire picture.

Other newborn infants appear normal until they attempt to nurse. This procedure usually precipitates respiratory embarrassment with cyanosis. Our first infant nursed apparently without difficulty for a few times. However, on the fourth day, after obtaining some milk by nursing, it became markedly cyanotic.

Whether the condition becomes manifest at the original respiratory efforts or whether it follows ingestion of food, cyanosis and grunting labored respirations appear. Physical examination of the chest will disclose the above signs and the diagnosis can be immediately proved by x-ray.

SUMMARY AND CONCLUSIONS

1. A review of the literature reveals that congenital diaphragmatic hernia, formerly thought to be rare, is actually not rare.
2. Until 1935, treatment was generally considered to be useless. Since that time more than 60 per cent recovery has been reported as a result of adequate surgical interference. Thus early diagnosis and immediate treatment becomes imperative.
3. Two cases of congenital diaphragmatic hernia are reported.

We wish to express our thanks to Dr. O. S. Wyatt, who operated upon both infants, for permission to include his findings in this report.

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DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—In the University Hospital Clinic we have had two instances of diaphragmatic hernia. Neither were recognized and both finally were diagnosed only at autopsy. In each case the obstetrician and the chief of the department of pediatrics tried to make a diagnosis.

As I get older I am impressed with the many things that we used to consider undiagnosable and certainly uncontrollable, but which are now detectable by the recently discovered clinical signs, like those described by Drs. Haugen and Ehrenberg. In these two cases which we had, if these facts that they have brought out had been known, we would certainly have suspected diaphragmatic hernia.

DR. PHILIP F. SCHNEIDER, EVANSTON, ILL.—The conditions described in this paper are encountered sufficiently infrequently so that I should like to include one case which came to my attention twenty years ago at the Evanston Hospital. Although the heart beat was present for some time after delivery, the apex beat was located to the right of the midline and respirations could not be induced. No autopsy was permitted, but x-ray of the chest revealed the left chest cavity completely filled with intestines, and the mediastinum displaced almost to the midline with apparent absence of the entire diaphragm on the left side. The x-ray findings in this particular instance, even though death had occurred, were of considerable significance.

DR. HAUGEN (closing).—The point regarding the frequency of multiple congenital defects is well taken. Fortunately in these two cases there were no other defects present.

PREGNANCY IN THE SYPHILITIC MOTHER

A STUDY OF 935 PREGNANCIES AT THE COOK COUNTY HOSPITAL*
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THE bad results for a pregnancy occurring in a syphilitic mother are well known. That these ill effects can be prevented by careful prenatal therapeutic procedures has been established beyond a question of a doubt. It is the purpose of this essay to present the results of therapy in a large series of cases from the Cook County Hospital obstetric department. In 1937 the writer, in collaboration with Dr. Hillis,¹ presented a review of a series of 418 cases, part of which has been incorporated in this study which, together with the 517 cases observed since the first series, create a total of 935 cases.

With the advent of syphilis control programs, congenital syphilis should practically disappear within one or two generations. The aim of antisyphilitic legislation has been attained in Denmark² where antisyphilitic legislation has been in effect since 1790. Following World War I in 1919, the number of new cases reported each year in Copenhagen had dropped from 3,000 in 1919 to less than 200 in 1933. Congenital syphilis naturally was proportionately infrequent.

RESULTS OF SEROLOGIC REACTIONS

At the Cook County Hospital prenatal clinic, all expectant mothers have had routine blood serologic examinations since 1929. The routine required that a patient with a positive serology reaction have a repeat test. If a weak reaction was noted, a provocative test was performed before therapy was instituted. The results of an earlier study revealed a degree of variation of opinion as to the dependability of the serology reactions in pregnancy.

Nakayama³ after exhaustive studies in pregnant mothers concluded that the blood serology reaction was of very little value in the diagnosis of syphilis. He was of the opinion that the parturient function creates a change in the reactive substance. Wile and Shaw⁴ believed that false positive reactions in pregnancy were negligible. Lawrence⁵ investigated the clinical significance of 839 incomplete Wassermann reactions and found clinical symptoms in 70 of 250 cases with weak positive reactions. Spiegler,⁶ on examination of 6,580 pregnant women, found that non-specific reactions (false positive⁵) occur in pregnancy no more fre-

*Presented at the regular meeting of the Chicago Gynecological Society, October 17, 1941.

quently than in the nonpregnant state. During the past five years at the clinic of the Cook County Hospital as much significance has been attached to a weak serologic reaction as to the complete reaction.

Each patient was interviewed carefully for a history suggestive of syphilis and attempts were made to obtain a report on the husband's Wassermann reaction. A previous survey had disclosed that among pregnant patients who had weakly positive reactions and were not treated, 3.5 per cent of these pregnancies resulted in syphilitic complications. This led to a careful search for other evidence of syphilis, such as the husband's Wassermann reaction, history of secondary lesions, previous stillbirths, premature labor and late abortions. When a suggestive history was obtained, therapy was instituted, despite the realization that an occasional patient would be treated unnecessarily.

TABLE I. RESULT OF SEROLOGY TESTS (WASSERMANN AND KAHN)

A Comparison of Reactions During Pregnancy and at Six Weeks Post Partum in 177 Cases

(All new cases without previous therapy)

Series 1.	Reaction weak or negative during pregnancies but strongly positive at 6 weeks post partum, despite therapy	29
Series 2.	Reaction strong in pregnancy but negative or weak post partum	40
Series 3.	Reaction strong during pregnancy and post partum	86
Series 4.	Reaction weak during pregnancy and post partum	22
Total		177

Table I reveals a survey of the intensity of serologic reactions in 177 cases. All tests were made at the Chicago Board of Health laboratories and included both Wassermann and Kahn reactions. The 177 patients had received no treatment prior to the pregnancy, and received a minimum of five to a maximum of twenty treatments before delivery. The inconsistency of the results as disclosed in Table I corroborates the belief that weak serologic reactions during pregnancy must receive the same degree of importance as the stronger complement fixations.

INCIDENCE

Estimates of the incidence of syphilis among prenatal patients vary. Reports from clinics among the colored in the south have revealed incidences as high as 30 per cent with variations to 3 and 5 per cent in other parts of the country. With an increase in legislative and educa-

TABLE II. INCIDENCE OF SYPHILIS AMONG PRENATAL PATIENTS BASED ON SEROLOGY REACTIONS

YEAR	TOTAL PATIENTS	SYPHILITIC	INCIDENCE
1932-1936	10,016	418	4.17%
1940 to April 1, 1941	3,325	125	3.76%

tional programs, the incidence should gradually decline. The results of such programs have already brought a reduction in the clinic at the Cook County Hospital.

Table II reveals a 9.8 per cent reduction in the incidence after an interval of four years.

This reduction in incidence is all the more striking since many patients are now being referred to the clinic from other agencies for therapy and delivery after the diagnosis has been made.

MODE OF INFECTION

The mechanism by which the fetus becomes infected is not clearly understood since it is possible for a syphilitic mother to give birth to a nonsyphilitic infant. Twenty-three of 50 untreated mothers in this series and 26 of 70 in the previous series gave birth to nonsyphilitic infants. With the advent of the Wassermann reaction, older concepts of the transmission of the infection have been discarded. Profeta's law and Colle's law are no longer tenable.

Cooke⁷ presents a logical and plausible explanation which our experience has tended to confirm. Cooke is of the opinion that when the initial infection occurs during pregnancy the extensive spirochetemia occurring during the primary and secondary stages of the disease always infects the placenta and then the fetus. However, since the infection has passed the acute stage in most pregnant mothers, the infant may not be infected. Transmission is dependent upon active spirochetes in the blood stream and, therefore, Cooke believes that transient periods of spirochetemia occur in cases of latent syphilis and that these periods of spirochetemia become less frequent as time passes on. If a period of spirochetemia occurs during pregnancy, then the fetus becomes infected. It is interesting that many syphilitic mothers have never had clinical manifestations of the disease and give no suggestive history. Cooke suggests that such a patient may acquire the infection from her husband long after he has received his initial infection and that the spirochete lies dormant in the testicle and is transmitted to the mother by means of the semen. Entering the mother in a dormant state, the spirochete does not produce the active manifestations of the primary or secondary stage, but remains dormant in some organ in a latent or attenuated state. The chances of transmission from mother to infant have been quoted as from 100 per cent to 50 per cent.

Since it is impossible to predict when a period of spirochetemia will occur during a given pregnancy, the object of therapy should be toward maintaining an adequate amount of germicidal agent in the blood stream at all times throughout the duration of the pregnancy. Patients with longstanding untreated syphilis stand a better chance of giving birth to a nonsyphilitic infant than do patients with a recent syphilis. Also patients who acquire primary lesions during later months of pregnancy may not necessarily have the syphilis transmitted to the fetus, and patients with secondary lesions untreated should have almost 100 per

cent transmission to the pregnancy. Third generation syphilis should be rare, if a possibility at all.

TREATMENT

Following a diagnosis of syphilis, the patient is instructed to report to the antisyphilitic clinic once per week throughout the pregnancy. In addition to the routine prenatal management they are given intensive antisyphilitic therapy consisting of the administration of 0.6 Gm. of neoarsphenamine intravenously and 0.13 Gm. of bismuth salicylate intramuscularly every week until delivery. In selected cases, because of technical difficulties, 0.2 Gm. of bismarsen is administered intramuscularly as a substitute. There are no rest intervals during the prenatal period. This plan of management is carried out with the advice and cooperation of the department of dermatology of the hospital, and in the event reactions occur or there is a question of modifications or variations of treatment, the dermatologists are consulted.

A ward, nursery, and delivery room separate from the remainder of the maternity division are set aside for the delivery of these patients. At the time of delivery or shortly thereafter, all infants are examined for evidence of syphilis. Hinrichsen,⁸ in an exhaustive review on the interpretation of modern serology tests, mentions the conclusions of Roby and Lembcke that the cord Wassermann reaction reflects almost exactly the condition of the mother's blood at the time of labor and that the substance causing the positive reaction passes completely out of the child's blood within two months. Since a negative cord blood reaction is valueless in a treated mother and a positive reaction is of no significance as far as the infant is concerned, the practice of routine cord blood reactions had been discontinued many years ago.

All infants and stillbirths are x-rayed for evidence of syphilis of the long bones. Autopsied infants are examined intensively for evidence of syphilis, including microscopic examination of the metaphysis of long bones by the pathology department. If no evidence of syphilis is found, the patient is instructed to return to the clinic with her baby six weeks post partum, at which time blood specimens are obtained from both mother and child for serology reactions. Roentgenograms of the long bones of the infant are taken at the six-week period and are repeated at three months, six months, and one year whenever possible.

If at any time syphilis is suspected or diagnosed, the infant is referred to other agencies for therapy. The mother is offered therapy for one year following delivery. It is noteworthy that 17 per cent of all patients return pregnant again within one to two years. All patients before discharge are urged to resume treatment whenever they become pregnant. The 935 pregnancies occurred in 722 women.

RESULTS OF TREATMENT

The results of therapy are divided into "failures" and "salvaged." The failures include all abortions beyond the fourth month; premature labors of macerated and nonmacerated syphilitic fetuses; all stillbirths and neonatal deaths, and all infants who after delivery present evidence of congenital syphilis. Although not all of the macerated fetuses can be charged to syphilis, nevertheless they are considered as failures because of the maternal syphilis. Salvaged cases include all infants followed for at least six weeks who do not present evidence of congenital syphilis. It is admitted that a few of the salvaged cases may sometime later in life present evidence of syphilis, but the difficulty of follow-up for more than one year limits the recording of such cases.

The statistics reveal that only 39 per cent of all untreated mothers will have the infection transmitted to the fetus. Antisyphilitic therapy during pregnancy, although carrying a failure of 6.7 per cent in the entire group, compares very favorably with 39 per cent of syphilitic pregnancies in the untreated group (Table III). The total salvages in

TABLE III-A. RESULTS OF 517 CASES OF SYPHILIS—TREATED AND UNTREATED (PRESENT SERIES)

AMOUNT OF TREATMENT	5 OR LESS	6 TO 10	OVER 10	NONE	TOTAL
Live, nonsyphilitic infants	125	103	213	76	517
Failures, including stillbirths, syphilitic infants, abortions	9	9	12	28	58
Percentage salvaged	92.8	91.3	94.4	63.2	
<i>Results of 418 Cases—Previous Series</i>					
Live, nonsyphilitic infants	106	105	137	70	418
Failures, including stillbirths, syphilitic infants, abortions	12	9	3	30	54
Percentage salvaged	88.7	91.5	97.9	57.2	

TABLE III-B. SUMMARY TOTAL CASES—BOTH SERIES

Treated cases	789
Failures	54
Percentage salvaged	93.3%
Untreated cases	146
Failures (syphilitic pregnancies)	58
Percentage	61.0%

both series are remarkably consistent. The results achieved among the patients receiving more than ten treatments are especially noteworthy. There were 15 failures in 350 cases. This will be given further consideration.

Table IV demonstrates the efficiency of intensive therapy, particularly when the parturient individual receives more than ten treatments during pregnancy. Better results are to be expected in those patients given even a minimum amount of treatment than among the untreated patients. A comparison of both series of cases reveals conclusively that in

TABLE IV. A COMPARISON OF RESULTS AMONG 608 NEW CASES PREVIOUSLY UNTREATED AND 327 OLD CASES PREVIOUSLY TREATED

<i>New 354</i>					<i>Old 163</i>			
NUMBER OF TREATMENTS	1-5	6-10	10 OR MORE	NONE	1-5	6-10	10 OR MORE	NONE
<i>New Series</i>								
Number of cases	86	71	147	50	39	32	66	26
Failures	6	6	11	23	3	3	1	5
Per cent salvaged	93.1	91.6	92.6	54.0	92.6	90.7	98.5	82.0
<i>New 254</i>					<i>Old 164</i>			
NUMBER OF TREATMENTS	1-5	6-10	10 OR MORE	NONE	1-5	6-10	10 OR MORE	NONE
<i>Old Series</i>								
Number of cases	63	61	90	40	43	44	47	30
Failures	8	3	3	20	4	5	0	10
Per cent salvaged	87.2	95.1	96.7	50.0	90.7	88.7	100	66.0

patients receiving adequate therapy, particularly in patients who have received treatment before pregnancy, congenital syphilis can be completely prevented.

In order to analyze the results of therapy, the failures were classified as to termination in the recent series of 517 cases.

TABLE V. SUMMARY OF FAILURES (517 CASES IN RECENT SERIES)

	ABORTIONS (4 months)	STILLBIRTHS	NEONATAL DEATHS	BORN ALIVE WITH SYPHILIS
Untreated 76 patients	8	10	7	3
New patients treated (354)	5	9	3	2
Old patients treated (163)	6	5	0	0

All syphilitic mothers whose pregnancies terminated beyond four and one-half months of uterine gestation in macerated fetuses in the absence of other maternal complications were considered as syphilitic. An average of two treatments was given the 11 mothers whose pregnancies terminated in abortion. In the 9 new cases in the stillbirth group, 3 mothers received more than 10 treatments, but in the older patients treated only 1 of 6 received adequate therapy. In the group of 3 neonatal deaths, 1 infant weighed 2 pounds 10 ounces, the mother receiving only 3 treatments; the other 2 infants were over 5 pounds and in one instance the mother received 10 treatments. In all cases a positive diagnosis of congenital syphilis was made either pathologically, serologically or roentgenologically.

In 4 of the failures the mothers received bismarsen intramuscularly because of technical difficulties in giving intravenous therapy. One of these patients received approximately 30 injections and, although born alive, the infant had syphilis. In the other three cases, one patient received 3, another 8, and the third 7 bismarsen injections. All of these

pregnaneies terminated in stillbirths. Only 30 patients received bismarsen during pregnancy and 4 failures are recorded. These cases are included in the tables presented and demonstrate the importance of intravenous therapy.

FOLLOW-UP AND THE DIAGNOSIS OF CONGENITAL SYPHILIS

As stated previously, an attempt is made to follow infants for at least one year. However, since the second series of cases was begun, additional social agencies have been available for follow-up, and thus it was possible to learn of nearly every case of congenital syphilis among the babies delivered whose mothers failed to return them for follow-up. At the present writing 95 per cent of all infants delivered during the past year are returning to the clinic for periodic check-up.

A positive serology reaction beyond the eighth week of life establishes the diagnosis of congenital syphilis beyond a question of doubt.

Roentgenologically the earliest characteristic lesion seen is a syphilitic osteochondritis (a definitely widened epiphyseal margin and a rarefied submetaphyseal zone). It is this finding that has caused much confusion in the diagnosis of early congenital syphilis. Dr. Philip Aries⁹ of the pediatric department, after a study of 300 roentgenograms taken of infants born of syphilitic mothers at the Cook County Hospital, has helped clarify the value of roentgenologic manifestations in the diagnosis of early congenital syphilis and believes that a positive diagnosis must be made with extreme caution.

With the results of therapy as shown in this paper and as reported from numerous other clinics, in the absence of positive serology in the infant, the attending physician should not rely in toto on x-ray findings and early serology reactions, but should seriously consider the amount of therapy given the mother during pregnancy before making a diagnosis of congenital syphilis.

THIRD-GENERATION SYPHILIS

Cases have occasionally appeared in the literature of third-generation syphilis. Twenty cases of known congenital syphilis were followed in the clinic and delivered in the hospital. Eighteen patients had received therapy for various periods before pregnancy. Sixteen patients received adequate treatment during the present pregnancy, and 4 received inadequate treatment. However, one case is of special interest.

The patient, A. J., aged 18 years, colored, married one year, had no previous serology tests and was seen for the first time in the fifth month of pregnancy. She had the typical Hutchinson's teeth and the Kahn and Wassermann reactions were 4+ positive. The mother of this patient was interviewed and it was learned that she had been married twice. The patient was the child of her first marriage. Five years after the birth of this child she was told she had syphilis and was treated for five months. Her first husband had also been taking "shots." Her second

husband had a negative Wassermann reaction. The patient was not treated during this pregnancy and gave birth to a seven-pound female which to the present time has been serologically and roentgenologically negative. It would have been surprising if the infant had had syphilis.

FIVE-DAY INTENSIVE THERAPY

The incidence of tragedies for the pregnancy among patients who have secondary lesions during pregnancy is extremely high. In 9 such patients, there were 5 failures; 2 abortions, 2 macerated stillbirths, and 1 infant congenitally syphilitic. Only 2 of the 5 failures received adequate therapy. The thought that these failures could be prevented by massive dose arsenotherapy over a five-day period seemed worthy of trial. With the cooperation of the dermatology department, under the direction of Dr. H. Rattner, 8 patients have been treated by this technique (2 with primary lesions and 6 with secondary lesions).

The first patient with a primary lesion near the fourchette was admitted to the hospital at term; continuous therapy was administered at once and after forty-eight hours of therapy the patient delivered a live, nonsyphilitic infant. The mother received 480 mg. of mapharsen (240 mg. of arsenic) before delivery. The infant showed no deleterious effects and chemical analysis of the infant's blood on the fifth day of life revealed 0.0005 mg. of arsenic per cubic centimeter of blood specimen. The blood chemistry of the mother revealed 0.0006 mg. per cubic centimeter of blood specimen. A second patient, one with secondary syphilis, eight months pregnant, was given five days of intensive therapy (1200 mg. of mapharsen). She returned one month later and delivered a seven-pound nonsyphilitic infant. This baby at two and a half months is still negative. The mother is showing evidence of becoming seronegative. Shortly after delivery the blood of the mother revealed 20 Kahn units; the baby's blood was negative.

Two additional patients have delivered nonsyphilitic infants. One patient aborted in the third month of uterine gestation several days after completing therapy, and the remaining three are still undelivered. One of these undelivered patients had a primary lesion and was treated during the second month of pregnancy.

In these 8 patients treated intensively, 5 have revealed serologic improvement and 3 complete reversal. This small series of cases suggests that this new method of attack in properly selected cases may be harmless to the fetus and yet offer promise for therapy in the acute stage of syphilis during pregnancy. This method of treatment requires further investigation to evaluate properly the fetal results and the danger to the mother. Great caution must be exercised in treating these mothers and therapy must be stopped at the slightest evidence of reaction.

REACTIONS

During the earlier series of 416 cases, there was one maternal death due to an arsenical exfoliative dermatitis. In the present series of 517 cases there were no deaths associated with therapy. Greater care has

been exercised in deferring treatment in patients who develop dermatosis of the slightest degree, albuminuria, elevated blood pressure or temperature. Severe reactions are infrequent. Nausea and vomiting two to four hours following the injection seem to be most frequent. No nitritoid crises or cases of yellow atrophy have been observed. Occasionally a mild syncope has been noted, but this has usually been on a psychic basis. Opinion differs in the literature as to the prevalence of reactions.

Cole,¹⁰ in presenting the results of the Cooperative Clinical Group studies, concludes: "The pregnant syphilitic woman is a good risk for arsenical therapy," after analyzing the reaction incidence in 4,600 injections given to 603 expectant mothers at five university clinics. Stokes,¹¹ however, is of the opinion that the pregnant woman is not a suitable candidate for strenuous treatment regimens and that any sign of reactivity should be taken more seriously than in the normal cases. Ingraham,¹² comparing the reaction incidence among cases at the Philadelphia General Hospital with those of the Cooperative Clinical Group, finds a much higher incidence of reactions; "in pregnant women, nausea, vomiting and diarrhea are three and a half times more frequent than in the nonpregnant; jaundice two times more frequent and evidence of kidney strain sixteen times." He presents seven deaths in pregnant patients receiving arsenic therapy and analyzes 35 additional cases in the literature, two-thirds of whom died of acute encephalopathies. Plass and Woods¹³ reported three fatalities due to arsenical hemorrhagic encephalitis and conclude that the pregnancy makes the syphilitic patient more susceptible to the deleterious effect of arsenic. Paley and Pleshette¹⁴ report a single case of hemorrhagic encephalitis in 1,200 treated prenatal patients at the Harlem Hospital; they found 158 cases of hemorrhagic encephalitis following arsenic therapy reported in the literature. They suggest using small doses initially and stopping therapy when headache, dizziness, or generalized pains begin. Since capillary hemorrhage is the essential pathology in hemorrhagic encephalitis, they suggest the administration of vitamin K and calcium during the period of therapy.

It is noteworthy that in all the cases reported as having developed encephalopathies, the initial reaction occurred shortly after the first, second, or third injection. In view of the number of cases reported we have been most fortunate in having experienced none of these complications. The only possible explanation for this lack of serious complications in our patients is that therapy is stopped without hesitation in the presence of a temperature of 99.2° F., a trace of albumin in the urine, elevation of blood pressure readings to 140/90, the presence of mild upper respiratory or other infections, the slightest pruritus, local or generalized, and finally if the patient reports severe or persistent vomiting after any single injection. The results we have obtained tend to confirm the contention that the pregnant syphilitic tolerates arsenotherapy as well as the nonpregnant patient.

CONCLUSIONS

1. The results in a total series of 935 pregnancies occurring in syphilitic mothers are presented; 789 of these patients received therapy with a 93.3 per cent salvage; 146 mothers were untreated and only 61 per cent gave birth to apparently nonsyphilitic infants.

2. Among 350 patients who received adequate therapy, all but 15 pregnancies terminated satisfactorily.

3. Patients receiving therapy both prior to and during pregnancy have almost a 100 per cent chance of having a nonsyphilitic infant.

4. All patients with a history of syphilis should be treated during each pregnancy without consideration of serologic reactions or amount of previous therapy.

5. Serologic reactions during pregnancy present a degree of inconsistency. When weak reactions are repeatedly observed, therapy should be instituted, especially if a history is obtained of stillbirth or late abortion, suspicious lesions, or a positive reaction in the husband.

6. Germicidal agents to be effective must be administered intravenously.

7. Third generation syphilis is an extremely rare condition.

8. Intensive therapy during pregnancy requires additional investigation, but from the little experience presented apparently is a harmless procedure in properly selected cases and offers an excellent prospectus for the pregnancy in a patient acquiring a primary lesion or developing secondary lesions during pregnancy.

9. In the absence of positive serology reactions in the newborn, consideration should be taken of the amount of treatment given the mother during pregnancy in making a diagnosis of congenital syphilis.

10. The dangers of arsenic therapy for the mother must always be considered, and therapy should be stopped at the slightest indication that a reaction may be imminent.

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DISCUSSION

DR. PHILIP L. ARIES.—The syphilitic pregnant woman who has not been treated adequately during her pregnancy may give birth to a baby that appears normal, or to one that has clinical manifestations of hereditary syphilis during the neonatal period. The latter condition makes the prognosis for life poor, for the infant rarely survives the first weeks or months of life in spite of careful anti-syphilitic management. The normal-appearing newborn, if infected with the spirochete, may present no clinical or serologic evidence of syphilis until the fourth to eighth week of life, and in a few instances not until much later. Obviously, it is desirable to institute specific therapy in these infants prior to the development of clinical manifestations, but unfortunately it is often difficult to make a definite diagnosis. The serologic diagnosis, the search for placental pathology, examination of the umbilical vein scrapings for spirochetes, and roentgen ray examination of the long bones for evidence of syphilitic osteochondritis all have their limitations. A careful follow-up period of observation for six months to a year is essential before the ultimate conclusion, that a child is free from hereditary syphilis, can be reached.

A positive Wassermann reaction in the early weeks of life may result from antibodies transmitted from the mother. A positive reaction which becomes less positive, then negative, by the eighth week of life may be found in the noninfected child. Positive evidence of osteochondritis as revealed by the roentgen ray examination of the bones of the newborn is the most reliable criterion upon which the diagnosis of hereditary syphilis can be made. Experience in reading films, however, is essential, otherwise changes from the usual but still within normal limits may be called positive. On the other hand, negative or suggestive findings in the roentgenograms may become definitely positive when the bone is re-rayed after the child has reached the eighth week of life.

After observing the patients for several years, we can accept Dr. Benenson's conclusion that a syphilitic mother, adequately treated during pregnancy, that is weekly from the fifth month and through the last trimester, has practically a 100 per cent chance of giving birth to an infant free from inherited syphilis.

DR. HERBERT RATTNER.—During the past year in the department of dermatology at the Cook County Hospital, we have treated 270 patients with early syphilis by means of the five-day massive dose technique. About one-third of them have been women ranging in age from 16 to 49 years. We administer to each patient daily, regardless of age, sex, or weight, 0.24 Gm. of mapharsen dissolved in 2,000 c.c. of 5 per cent glucose solution. In five days a patient receives 1.2 Gm. of mapharsen. In our case the solution is administered in a vein of the hand and allowed to flow at the rate of about 40 to 50 drops per minute. No special preparation of the patient is necessary, but we have been careful to select only healthy persons. The experience is perhaps none too pleasant for many of the patients, but it is not a great hardship. Most of them suffer from headache, nausea, vomiting, fever, and pain in the arm for the first day at least, but in general the reactions are minor ones. In three instances, however, we have encountered alarming reactions. There were two cases of toxic encephalopathy and one patient in whom there developed acute glomerulonephritis, hepatitis, ileus, and pericarditis. There have been no fatalities in our group.

The results so far as can be judged this early have been satisfactory. The best results were obtained in the patients who reported for treatment very early. In those with seronegative chancres, the "cures" were apparently 100 per cent. In those with late secondary eruptions the incidence of cure has dropped to about 87 per cent. We have retreated 12 patients either because of reinfection (2 undoubted cases), relapse or superinfection without any harmful effects. Among our patients

there were 10 pregnant women with early syphilis, 5 of whom have delivered apparently healthy infants, the oldest now eight months of age. The other women are awaiting delivery.

In the past few weeks, with the cooperation of Dr. Benensohn, we have undertaken to treat pregnant women with untreated latent syphilis. The same dosage has been used, regardless of the stage of pregnancy. One of our women, as Dr. Benensohn related, was at term when she reported with a chancre. Others were in the second, third, fifth, seventh, and eighth months of pregnancy.

The method of treatment, of course, is a radical departure from the standard methods now in use. The results of the first cases treated in New York in 1933 have been excellent. This has encouraged us because our early results are running a curve that parallels that of the results of the New York group. Were it not for the cases of encephalitis that have occurred (one in about every 200 cases), the method of treatment would be generally adopted. For the present it must still be considered as in the experimental stage until more cases have been treated for a sufficiently long time to allow statistics to tell the complete story.

DR. RICHARD FRANK.—I would like to present a few figures from the syphilitic patients at the Chicago Maternity Center during the last two years. For reasons of comparison I would like to show that the incidence of syphilis in women in Chicago was 2.1 per cent in white women and 14.9 per cent in colored women among a group of approximately 14,000 women examined during 1939. In the two-year period from July, 1939, to June, 1941, 3,051 white women were delivered at the Chicago Maternity Center, with an incidence of 1.6 per cent syphilis (48 patients) and 1,802 colored patients with an incidence of 5.3 per cent syphilis (95 patients).

As to the amount of treatment during pregnancy: Each patient received an average of 11.4 arsenical injections and 17.4 injections of bismuth. That includes those who were put under treatment during the first month of pregnancy as well as those who came in during the last few weeks of pregnancy and had only three or four injections before delivery. Actually 63.7 per cent of all patients received treatment before the fifth month. Each one received an average of 14.2 arsenical injections and 23.7 bismuth injections.

I would just like to bring out one point that Dr. Benensohn did not stress—the importance of early treatment in pregnancy. The treatment must begin before the fourth month. It must go on with strict regularity on a weekly schedule if good results are to be obtained.

Dr. Benensohn mentioned the theoretical presence of spirochetemia all through pregnancy. We do not know if, when and where this occurs, but the only way we might fight it is by maintaining continuously a certain level of a spirocheticidal arsenical in the patient's serum, in order to protect the baby.

As to the results of syphilis treatment in pregnancy: Of 142 patients delivered, 124 have been followed from three to twenty-seven months, and 86.7 per cent have shown no signs of syphilis up to the present time. There was no syphilitic stillbirth, the 9 fetal deaths (early and late pregnancy and neonatal) being due to obstetric complications. Autopsy in these cases did not reveal any syphilitic changes. There was one baby with syphilis of a mother who received only 4 injections and was treated for only three weeks. Six and three-tenths per cent of the babies were not followed up because they could not be located.

DR. I. M. LEVIN.—The excellence of prenatal care at the Cook County Hospital has markedly reduced the incidence of congenital syphilis on the obstetric service. This has resulted in a paucity of material for the venereal service of the Children's Hospital in which we have pioneered with intensive massive intravenous arsenotherapy, the so-called "five-day treatment."

The work of Synder and Speert in 1938 in demonstrating that arsenic is deposited in the placenta of rabbits at the period of viability has many implications. No arsenic is found in the fetus prior to this time, and the concentration in the placenta exceeds by many times that in the fetus. The logic of arsenotherapy after the fourth month of pregnancy is self-evident.

Certain features of serologic reaction in mother and child are commonly overlooked. The mother may give a positive Kolmer and the infant a negative, and vice versa. In neither instance is syphilis ruled out. Serologic negativity on the part of the mother does not preclude syphilis in the child. Cord blood serology is that of the mother at the time of delivery and is not conclusive for the infant.

Quantitative serology is a distinct advance in our diagnostic field. A Kahn titer of higher unity value in the infant than in the mother is almost conclusive evidence of congenital syphilis. Where the child's titer is lower than that of the mother this may be a transmitted serologic reaction, which may disappear within four to eight weeks and the child be free of syphilis. On the other hand after a period of negativity it may again begin to rise, evidence of spirochetal activity and active infection.

It is not easy to make a diagnosis of congenital syphilis. There may be no clinical physical signs. Prior to the work of Caffey and Aries, we thought we could employ bone x-rays as presumptive evidence of syphilis in a very high percentage of infants. We now know that nutritional disturbances, rickets, scurvy, and a variety of disorders may simulate syphilis. Only a positive Wimberger sign (symmetrical osteomyelitis of the medial upper third of the tibiae) is conclusive.

Insufficient attention is given to gross and microscopic examinations of the placenta and cord for evidence of syphilis. Such studies in addition to roentgenographic and serologic examinations should yield the highest percentage of positive diagnoses. Early affirmative evidence of syphilis will make possible the treatment of congenital syphilis at the earliest possible time when massive intravenous arsenotherapy is most effective.

Liston, W. Glen: *Trichomonas Vaginalis* Infestation, Brit. J. Ven. Dis. 16: 113, 1940.

The author goes into great detail concerning the morphology and species differentiation of the trichomonas parasite. There can be no doubt that the species of trichomonas which are found in man inhabit specifically selected sites.

T. vaginalis has never been found free in nature, and it is a parasite strictly confined to man. It is difficult to know how infection spreads. Carrier cases are numerous, and may be a fruitful source of infection. In persistent cases the cause may be due to the fact that the parasite takes up an abode in and below, rather than on the surface of mucous membranes.

Glycogen in the vaginal epithelium seems to be necessary for the development of the parasite. It is stated that *T. vaginalis* flourishes in the degree of acidity favorable to a Type III vaginal flora, which comprises a great variety of organisms, but small cocco-bacilli predominate.

The author divides the disease into an acute, subacute, and a chronic or a latent form. The symptoms are well known.

The entire principle of treatment lies in eradicating the *T. vaginalis*, restoration of the glycogen to the epithelial cells, and the establishment of Doederlein's bacillus in the vagina. A cure is established when the pH returns to and remains at about 4. The author used carbarsone suppositories exclusively in his routine of treatment.

WILLIAM BERMAN

THE TREATMENT OF HYDROCEPHALUS IN CEPHALIC PRESENTATION

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THE following case history is deemed worthy of presentation and discussion because it illustrates a new method of treatment in cases of hydrocephalus which we believe is simpler than any previously proposed.

M. O'G., aged 20 years primigravida. Father and mother living and well. Four siblings living and well. She had had no familial diseases or no serious illnesses. Menstruation was normal. Last period occurred on Dec. 8, 1940, and delivery was due Sept. 15, 1941. The patient was seen in consultation by one of the authors (A. G.) on Sept. 8, 1941, with Dr. Joseph MacDonald at St. Elizabeth's Hospital, because of an increase in weight of 13½ pounds during the previous three weeks, an unengaged head, and vague abdominal pains. She was having mild uterine contractions occurring every fifteen minutes. A vertex presented and seemed to be enlarged. The lower uterine segment was rather tense. Fetal heart was in L. U. Q., position and rate was 130. No presenting part could be felt rectally. The cervix was closed and partly taken up. Diagnosis: Pregnancy near term. There was disproportion with a large head, and a question of hydrocephalus. X-ray films revealed a large head above the pelvic brim but the plates were not satisfactory. The patient's pains ceased and she was sent home for observation and re-examination in another week. She re-entered the hospital a week later in mild labor and with a slight bloody show. Rectal examination revealed a cervix 3 cm. dilated and partly taken up, with the membranes bulging through the os. The presenting part, however, could not be felt. The fetal heart was in L. U. Q. position, with a rate of 130. A vaginal examination was done and the membranes were ruptured. The presenting part was then made out to be a vertex which had the consistency of thick, soft, wet leather. Diagnosis: Hydrocephalus. X-ray examination revealed a hydrocephalic head and comparison with the rather unsatisfactory pictures of the week previous demonstrated that a definite increase in the size of the head had occurred during this period. The patient was anesthetized with nitrous oxide and oxygen and light ether anesthesia. The operative field was prepared with tincture of metaphen, sterile drapes were applied and the vagina was flushed with a solution of S. T. 37.* The cervix was exposed with retractors. It was 3 cm. dilated. The child was baptized, using a long glass syringe. A No. 18 gauge spinal puncture needle was easily inserted into the presenting part. Cerebrospinal fluid immediately spurted under pressure. About 1,400 c.c. of fluid were removed. After the initial pressure was released, the rate of flow slowed somewhat. Abdominal pressure on the head resulted in a satisfactory return of the flow through the needle. About twenty-five minutes were spent in allowing the fluid to drain. Labor began almost immediately. X-rays were taken after the tap was finished. It was noted toward the end of the tap, that the head, now greatly collapsed and softened, was rapidly dilating the cervix and coming into the pelvis. Labor lasted one hour. The patient delivered

*Hexylresorcinol solution.

normally. A small episiotomy was done. The child was born alive and lived for two hours. As soon as the child was delivered, intravenous ergotrate, $\frac{1}{320}$ gr., was administered. The placenta separated promptly and was expressed four minutes after delivery of the child. The episiotomy was sutured. The uterus reacted well. The patient's condition was excellent at the end of the delivery. Autopsy of the child revealed marked atelectasis, internal hydrocephalus, spina bifida with meningocele, dorsolumbar atrophy of the spinal cord, and cerebellar adhesions to the dura mater.

DISCUSSION

Current texts do not mention this form of treatment. Irving¹ recommends perforation and version. DeLee,² Piper,³ and Stander⁴ recommend the cranioclast if the natural forces are insufficient after perforation. Titus⁵ recommends perforation and the cranioclast with slow extraction. Kerr⁶ and Montgomery and Bland⁷ recommend perforation followed if necessary by forceps application. There is no complete unanimity of opinion because DeLee² and Oldfield⁸ believe that there is a slight risk of rupture of the uterus if version is attempted. Moreover, Eden and Holland⁹ and DeLee² believe that the cranioclast is inefficient because it is liable to slip. Practically all writers who go into any detail recommend that perforation be performed either at full dilatation or when the cervix is easily dilatable. It is evident from their statements that a good deal of labor must take place before perforation can be done. Titus⁵ further recommends, in Catholic patients, the performance of internal podalic version first and then craniotomy to the aftercoming head when the child is dead. Sehumann¹⁰ and Titus⁵ insist on the necessity of perforation plus a thorough evacuation of the cranial contents so as to ensure fetal death. Others, such as Jellett and Madill¹¹ do not insist on the latter.

A consideration of these recommendations makes it obvious that there is unanimity of opinion as to the desirability of perforation so as to ensure two things: (1) A head small enough to be delivered either normally according to some, or by operative means according to others. (2) The desirability of a dead baby, to the extent of direct infanticide in the opinion of some writers. There are, however, rather marked variations in the treatment after perforation and some of the procedures recommended require (1) deep anesthesia, (2) a not inconsiderable amount of training and skill, and (3) a good deal of either vaginal or intrauterine manipulations, or both. Moreover, these latter manipulations take place in a uterus whose lower segment has been subjected to a great deal of stretching both before labor and during labor, a situation not ideal for operative procedures. Again, many of the statements are prefaced by the remark that perforation should be done when the cervix is fully dilated or easily dilatable, a condition not always easy to attain in actual practice. Full dilatation in these cases occurs slowly, the labor often being very inefficient and prolonged. The patient is, therefore, subjected to a good deal of pain which should be obviated if practicable. In addition, the length of labor required for full dilatation can seriously overstretch an already markedly distended lower segment. As far as easy dilatability is concerned, the stretching of the cervix when the lower segment is greatly thinned out is conceivably not without danger. The recommendation of Titus⁵ that an internal podalic version should be performed when the patient is a Catholic, provided that the conditions are such that this is possible without risk to the mother, is, in our

opinion, impractical and dangerous. We do not believe that the proper conditions for version are ever present in these cases. We feel that the great size of the head and the marked thinning of the lower segment contraindicate version in all cases of hydrocephalus because of the great danger of rupture of the uterus. The latter has, in fact, occurred in the practice of one of the authors (C. T. O'C.).

We recommend intraventricular tap and drainage per vaginam with a spinal needle. This procedure has several advantages over those mentioned. (1) Often no general anesthesia will be found necessary, especially in multiparas. Morphia and scopolamine will suffice. At the most nitrous oxide and oxygen are sufficient. (2) No dilatation of the cervix beyond that required to introduce the needle, and therefore no prolonged labor is necessary. The procedure, therefore, does not add a long labor to the dangers of an already overstretched lower segment. (3) The maneuver can be performed by house officers and general practitioners, the men who still deliver most women. Finally, the method can be used on Catholic patients.

At a previous hospital staff meeting in March, 1939, when one of us (O'C.) reported a rupture of the uterus caused by an attempt at internal podalic version in a case of hydrocephalus, the method of Wilson¹² was suggested. This maneuver is applicable to Catholic patients. It was decided by both of the authors to treat the next case of hydrocephalus on our service or in private practice by intraventricular tap with a spinal needle per vaginam, rather than abdominally as recommended by Wilson. During the discussion, the Rev. Fr. Donald McGowan, the superintendent of the hospital, felt that if these procedures did not have as their purpose direct infanticide and did not kill the fetus, there would be no objection from the standpoint of Catholic ethics. It was decided to write to Wilson in order to find out if the tapping produced fetal death. His reply seemed to us conclusive. He states:¹³ "In those cases in which the fetal heart is heard when the head is on the pelvic floor, perforation is done to ensure the fetal death, and to facilitate extraction of the head." Later, Moore¹⁴ stated a Catholic viewpoint clearly: "The operation of craniotomy involves two stages: (a) perforation of the skull; (b) complete destruction of the cerebral contents." He goes on to say: "If the second stage of the operation is omitted and the physician attempts to effect delivery with as little loss of cerebral substance as possible and does all he can to save the life of the child, he is no longer making direct attempt to kill the child but in certain rare instances in which delivery may be otherwise impossible, he will be doing all he possibly can do to save the lives, both of the child and of the mother."

For those patients in whom the cervix is difficult to expose, or where the head cannot be brought within the reach of the needle per vaginam, tapping and drainage of the ventricle through the abdominal wall as advocated by Wilson^{12, 13} is suggested. The latter uses the procedure as a routine. His method may also be the procedure of election with trained obstetricians or in the rare case of hydrocephalus in a seriously ill patient, such as a Class III cardiac.

CONCLUSIONS

1. We believe that the simplest and safest method of treatment for hydrocephalus when it presents by the vertex is intraventricular tap and drainage per vaginam.

2. Intraventricular puncture abdominally as practiced by Wilson is recommended whenever introduction of a spinal needle through the cervix is difficult or inadvisable.

3. We believe that either of these procedures is superior to the recommendations in current texts, all of which require rather deep general anesthesia, more than a minimum of obstetric training and experience, and some of which are not without danger to the mother.

4. Intraventricular tap and drainage are permissible with Catholic patients.

The writers express their appreciation to the Reverend Francis B. Driscoll, Sister M. St. Clare, O.S.S., Sister M. Bonaventure, O.S.S., and Augustin W. McGarry, M.D.

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Chiray, M. M., Maschas, H., Mollard, H., and Baumann, J.: Spastic Colitis and Ovarian Disturbances, Presse méd. 48: 881, 1940.

The authors discuss the various pathogenetic theories of primary chronic spastic colitis in women. The review resolves itself eventually into a somewhat lengthy re-evaluation of two suggested conceptions. The etiologic factor may be found primarily in the intestinal tract *per se* or secondarily in ovarian hormonal aberrations. They note that chronic spastic colitis is not uncommonly found to be associated with such conditions as sterility, thyroovarian dyscrasias and varying degrees of more general symptoms, such as neurasthenia, neuralgias, myalgias, and generalized malaise.

The writers observe that the association of chronic spastic colitis and ovarian dysfunction appears to be more than coincidental. They were successful in treating both of the above symptom complexes with sex hormones. They used the estrogenic drugs, corpus luteum, and male hormone to secure relief for their 5 patients. These clinicians conclude that the sex hormones may play a role in the physiologic equilibrium of the intestinal tract.

CLAIR E. FOLSOME

A CASE OF UNRUPTURED TUBAL PREGNANCY DIAGNOSED BY GYNECOGRAPHY*

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THE inconstancy of the clinical picture of unruptured tubal pregnancy is universally recognized. If there is one reliable and dependable sign of this condition, it is the extreme tenderness found on palpation of the affected tube. When this sign is absent, as in the case reported below, the diagnosis is likely to be especially difficult. In this case, gynecography¹ (pneumeroentgenography) proved to be of such positive assistance in diagnosis that it assumed the deciding role. As this method of diagnosis is not commonly employed by the profession in ectopic pregnancy, and in order to call attention to its value in clinical diagnosis, this case report is made.

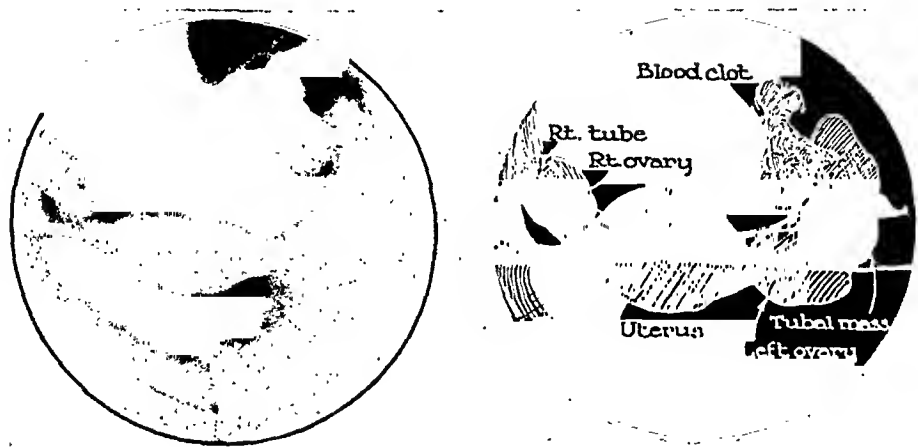


Fig. 1.—Unruptured tubal pregnancy (gynecography).

CASE REPORT

M. W., a 24-year-old woman, nullipara, married 2½ years, was first examined in the office Oct. 2, 1941. The history was that the menses, which had been regular 28-day type, 5-day moderate flow since the onset at age 11, were one week late in September, appearing on September 17, and then reappearing on September 26, accompanied by sharp left abdominal pain. The patient stated that contraception had been practiced until one month ago, and then intentionally interrupted. She gave a vague history of renal calculus last year.

Physical Examination.—The breasts were large, soft, but showed no typical evidence of pregnancy change. The uterus, normal in size, was retroverted and mobile. Both adnexa were *free from tenderness* and palpable swelling. The cervix was nulliparous, closed, and contained a

*Presented at a meeting of the Chicago Gynecological Society, October 17, 1941.

clear mucous secretion. Rectovaginal-abdominal examination revealed the same findings.

Pulse was 84; color, normal; blood pressure, 130/88; weight, 152 pounds. Urine showed a trace of albumin; no sugar; pH, 5.0; epithelial cells and occasional red blood cells in the sediment.

Tentative Diagnosis.—Suspected tubal pregnancy. Re-examination was advised in a few days when pregnancy tests were to be carried out. She was warned of possible danger and symptoms which might occur.

Four days later, October 6, she had an acute attack of pain in the left side during the night, and was sent to the Michael Reese Hospital by a neighborhood physician who also thought she had an ectopic pregnancy. Upon arrival at the hospital at 3:00 A.M., however, her pain had subsided and the abdomen was neither tender nor rigid. There was slight pink vaginal discharge. Examination revealed her pulse 92 (varied from 84 to 96), blood pressure 110/70, hemoglobin 70 to 80 per cent, red blood count 3,740,000, white count 14,000, and the urinalysis negative.

Bimanual examination revealed the same findings as in the first instance, complete absence of adnexal tenderness or mass, which made the diagnosis of tubal pregnancy questionable. The differential diagnosis to be made was: (1) tubal pregnancy, (2) intrauterine threatened abortion, (3) ureteritis or calculus, and (4) left corpus luteum cyst.

Various diagnostic procedures were considered and a decision was made to obtain a pelvic pneumogram using the transabdominal route (CO₂ inflation). The film (Fig. 1) accurately revealed the affected tube, showing the changes characteristic of tubal pregnancy. The shadow of both ovaries, uterus, and unaffected right tube appeared normal.

Laparotomy was performed through a Pfannenstiel incision, and an unruptured tubal pregnancy was removed. The similarity between the shape and size of the involved tube and the image which it produced on the x-ray film was indeed striking.

REFERENCE

1. Stein, I. F.: AM. J. OBST. & GYNEC. 43: 400, 1942.

310 SOUTH MICHIGAN AVENUE

THECA CELL TUMOR*

W. C. DANFORTH, M.D., EVANSTON, ILL.

IN RECENT years tumors of the Graafian follicle have been the subject of much study. While tumors of pure granulosa or theca type are not common, those in which granulosa cells predominate are far more numerous. In a recent report, Curtis stated that 33 theca cell tumors have been reported and added one to that number. In my service, a tumor predominantly composed of theca cells has been seen recently. In January, 1941, a private patient, aged 58 years, entered the hospital for the removal of a large pelvic tumor. Her menopause had occurred six years earlier. At 32 years of age a laparotomy had

*Presented at a meeting of the Chicago Gynecological Society, October 17, 1941.

been done. She believed that this was for pelvic inflammatory disease. No bleeding had been noted at any time since the menopause.

Examination disclosed a firm mass which extended four inches above the symphysis, somewhat irregular in shape, and movable. It was thought to be a myoma of the uterus.

Operation was carried out on January 31. A large, asymmetric, firm, pale left-sided ovarian tumor was found. The pedicle was quite short. The right ovary was normal. The uterus was of normal size. The left ovarian tumor was removed and a total hysterectomy done, leaving the adnexa on the right side. Recovery was uneventful.

The uterus contained a small intramural myoma, and there was a definite endocervicitis. The ovarian tumor weighed 635 Gm. The external surface was smooth and glistening. Sectioned surfaces were firm to slightly cystic, pale gray white, irregularly mottled yellow. The fluid in the cystic area was sticky.

Sections from the ovarian tumor revealed some areas composed of small, fusiform or stellate cells. The nuclei were small and fusiform. In some regions there was considerable pink intercellular substance which formed plaques. These areas were undergoing cystic degeneration. Some sections displayed numerous small cells, resembling theca cells which contained fat. This fat had an affinity for sudan III and stained black after fixation with osmic acid. Foot's modification of Bielschowsky's silver stain for fibrous tissue revealed a fine mesh of fibrous tissue surrounding the thecalike cells with a very delicate reticulum.

No hormonal stimulus was exerted by this tumor. In the series studied by Traut and Marchetti, a lack of hormonal influence was found in 28.3 per cent. Hormonal stimulus may vary with the age of the tumor and the proportion of cells of the theca type which a tumor contains. In this case the tumor, which was in an early stage of its development, had probably lost any hormonal effect which it might have had at an earlier stage of its growth. The large proportion of cells of the theca type would also lessen its endocrine activity.

It is difficult to draw an absolute line between the two types of tumors of the Graafian follicle, but those in which cells of the theca type predominate and those rather rare ones, which are of pure theca type, are benign. Of the granulosa group, it is estimated roughly that 10 per cent are malignant. In dealing with tumors of the theca type, the treatment need not be radical, a simple excision of the ovary in which the tumor is found being sufficient.

636 CHURCH STREET

Richard, A.: Plastic Removal of Redundant Abdominal Wall Tissue, *Zentralbl. f. Gynäk.* 64: 1542, 1940.

The author describes a trapezoid incision which he favors over the usual elliptical incision, as it allows more extensive removal of tissue and easier coaptation of skin margins. An incision slightly concave upward is made from one anterior iliac spine to the other. At a suitable distance above, another shorter parallel curved incision is made. The ends are connected by two short diagonally placed incisions completing the trapezoid.

R. J. WEISSMAN

Special Article

GRADUATE EDUCATION IN OBSTETRICS*

THE SEMINAR SYSTEM AS DEVELOPED IN PHILADELPHIA

PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

A SYSTEM of graduate education in obstetrics has been developed in Philadelphia in recent years through the medium of four committees. These committees study the various causes and surrounding circumstances of maternal deaths, stillbirths, fetal deaths, and premature births. The meetings, conducted as open seminars for the medical public, have been found to be an excellent type of extramural graduate education.

We had found that institutes or seminars conducted in county medical societies in Pennsylvania were unsatisfactory: on one hand from indifference of many members and, on the other, through difficulty in obtaining suitable teams of speakers to conduct these institutes. This was not due to a lack of obstetric qualifications as much as to their inability to interpret the problems of local physicians and to teach general practitioners.

Locally, intramural graduate education in obstetrics, through residencies and fellowships, with close clinical contacts in dispensaries, wards, and delivery rooms, has been most successful for the younger men. The Graduate School of Medicine at the University has offered for many years an excellent didactic and clinical course for men who have had a general obstetric experience and who desire polishing up for specialization.

The shorter intramural courses of one and two weeks in maternity hospitals have proved successful for graduates of moderate experience who wish to obtain new ideas and techniques for their practice, as well as to get a general freshening up on modern hospital methods. This system has been efficiently conducted in Philadelphia and Pittsburgh by the Commission on Maternal Welfare of the State Medical Society in conjunction with the Bureau of Maternal and Child Health of the State Health Department.

In order to obtain a full and all the year round discussion of various phases of obstetrics, we continued a closed analysis of maternal deaths as an open cooperative program between the hospital obstetric staffs of Philadelphia and the County Medical Society. Each month for seven years a representative of the various hospitals has voluntarily brought a complete record of any maternal death occurring in his hospital. A suitable abstract of the case on a printed folder is presented for our files. A discussion follows, with particular emphasis as to how such cases could be handled in the future to avoid the factors which influenced the fatal outcome.

*Read at the Thirteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, October 2-4, 1941, New Orleans, La.

As these discussions went on month by month, it was apparent that much bad obstetrics was being practiced. Corrective measures were taken to prevent unnecessary obstetric surgery or operative maneuvers in the hospitals by unqualified men. Keeping in mind the particular point of operative ability, most of the hospitals have rejudged their courtesy staffs, and have more clearly defined the privileges of the junior staffs. The hospitals accepted, in full or modified form, a detailed set of regulations governing the conduct of their maternity divisions. Chiefly, these cover rules for obligatory consultations and regulations for technique in labor, delivery rooms, and the nursery. Obligatory consultation before cesarean section in a large number of our hospitals has led, in my opinion, to a marked decline in the mortality from the operation, even though the incidence of the operation has shown a slight increase.

Through available funds, copies of such procedure books as that of the American Hospital Association and the regulations for maternity hospitals of the Chicago and New York Boards of Health, as well as various publications of the State Department of Health, and the Children's Bureau, have been sent to attending obstetricians of the hospitals. When the Committee on Maternal Welfare of the County Medical Society has made a specific recommendation regarding some particular situation, a mimeographed copy is sent to a large list of interested physicians.

In the monthly discussion of case reports much stress was laid for a time upon the presence and nature of avoidable factors. To avoid too much emphasis in an open meeting concerning responsibility and preventability, the hospital staffs have been asked to decide such points. Their decisions are noted upon the case study folder. This request necessitated the institution of individual hospital obstetric conferences. Mortality reports must be discussed at these conferences prior to the case presentation at the analysis meeting at the County Medical Society. The final presentations are made now by the interne or resident because of their manifested interest and intimate knowledge of the case history. A vote of the analysis group is taken regarding the preventability and responsibility of the death, when there is a general disagreement with the decision of the hospital staff.

As a result of these monthly seminars an obstetric conscience has been developed in Philadelphia.

Much of the material in the abstract files has been used in preparation of papers read before medical meetings. Assignments of topics to teams of younger men has served to cement their interest and act as stimuli in furthering graduate education in other groups.

As a consequence of this system of graduate education in obstetrics in Philadelphia, there has been a drop in the maternal mortality rate. This has fallen from 68 puerperal deaths per 10,000 live births in 1931, the year the study began, to 23 such deaths in 1940, a reduction of 67 per cent.

Since it was realized that fetal and neonatal salvage was germane to such a study, two committees were formed to investigate the stillbirths and neonatal deaths in Philadelphia. The first committee was organized under the auspices of the Obstetrical Society of Philadelphia. The second committee was developed under the auspices of the Department of Health, in order to bring the facilities of the Bureau of Vital Statistics

more closely into this work. These committees met separately for one year, studying their respective cases. Realizing their problems were largely similar, they merged meetings. It has not been possible to present for discussion every stillbirth and neonatal death. All cases are reviewed and tabulated by subcommittees. Four cases, with as far as possible the same basic cause, are presented by each committee at the monthly seminar. At a recent meeting 4 stillbirths and 4 neonatal deaths were reviewed, where in each instance the mother had been a diabetic.

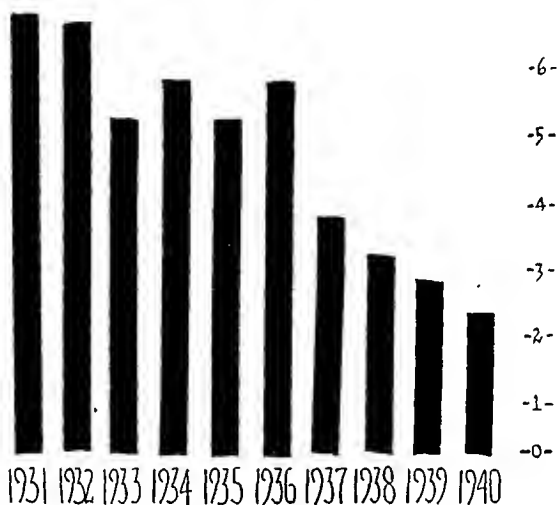


Fig. 1.—Puerperal (maternal) deaths per 1,000 live births.

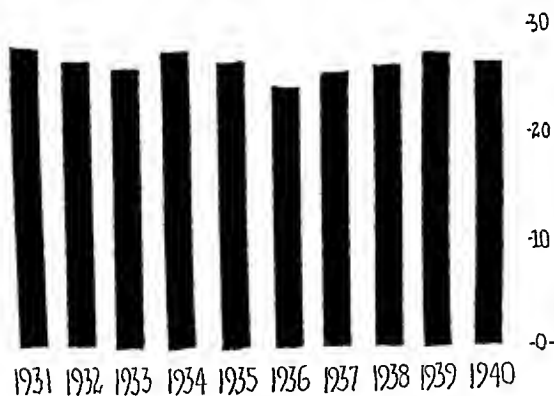


Fig. 2.—Neonatal deaths per 1,000 live births.

At another meeting, each death discussed had been in association with breech presentation, and, at yet another meeting, each mother had been extremely obese, two hundred pounds or more in weight. During the final fifteen minutes of each joint session of these two committees, a prepared résumé of the principal topic of the meeting, the basic cause of death, is given by a physician to whom the topic has been assigned previously. The pediatricians have shown a marked interest in these meetings, while the hospital pathologists have been helpful in discussing autopsy protocols. It was noted that a 50 per cent increase in autopsies in stillbirths and neonatal deaths occurred from the first to the third year of these studies,

The development of this second phase of our work broadened the base of the program on graduate education in obstetrics. The problems of prenatal care have been brought out more clearly. The study of the immediate neonatal period has been intensified. This expansion has resulted in reducing the stillbirth rate almost 40 per cent during the past few years.

A similar decrease has not been noted in the neonatal death rate. A review of the first two years' statistics of the neonatal study revealed that in one manner or another prematurity was the basic cause of death in over 50 per cent of such cases.

It was felt necessary to deal with prematurity as a special problem. Consequently, a new group has been formed to develop educational efforts along the lines of both cause and care of prematurity. Realizing that too many central meetings would probably nullify our efforts, the group interested in this problem has been made a traveling clinic. Each month the meetings are held in a different hospital. The obstetric and

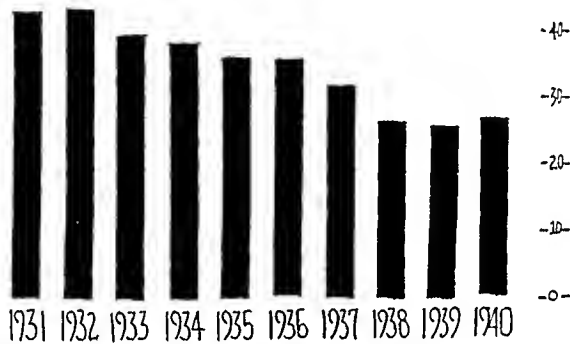


Fig. 3.—Stillbirths per 1,000 total births.

pediatric staffs of the hospitals, in turn, present the statistics of their premature births during the preceding twelve months, discuss the causes, their method of treating prematures, and demonstrate their equipment and personnel. But one such meeting is required to determine the qualifications of a hospital as a premature station.

These four committees form the basis of our extramural graduate education in obstetrics in Philadelphia. Continuously they present to the specialist, general practitioner and interne, the various problems and situations in obstetrics which call for mature judgment and skillful clinical technique. The discussions serve as a stimulus for more efficient study of cases in office practice and hospital clinic. There can be no doubt that the compulsory consultation service in hospitals has had a far reaching effect in providing timely and efficient therapeutic and operative help as well as avoiding much meddlesome midwifery.

Similarly, the problems of the fetus have been brought into sharp focus and the interest of the pediatric group has brought in line greater efforts to conserve the life of the newborn. Although the last committee, on the premature, has been in operation less than a year, its influence is being manifested in a widespread quickening of interest in this problem.

Graduate education in obstetrics, either intra- or extramural, will always be sought by the man who desires to improve his knowledge,

clinical experience and technique. Such a physician will get some good from almost any type of educational opportunity offered him.

Seminars at short intervals, voluntarily and cooperatively produced, can provide excellent instruction in the various phases of obstetric practice for men working in this specialty. A sustained interest has been maintained in our locality, with an average monthly attendance of over one hundred for our seven years. As evidence of the success of such a system of graduate education in obstetrics, we have noted a significant reduction in the maternal mortality rate; a moderate lessening of stillbirths and a determined effort on the part of all concerned to improve further our vital statistics.

The organizations of these committees signified no originality on our part. The analysis of maternal deaths follows closely the pattern of the Ohio Hospital Obstetric Society. The Stillbirth Study Committee uses the form employed by the Children's Bureau in their nationwide stillbirth study. Since the publication of their list of causes of stillbirths, we have used that manual in our classification. The Neonatal Mortality Committee uses the form popularized by Dr. Bundesen and the Chicago Board of Health. Finally, the Study of Prematurity, a joint committee of obstetricians and pediatricians, is along the same lines as that instituted about a year ago by the New York Board of Health.

DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—We are just over the threshold of another great movement in obstetrics and gynecology and that movement must become nation wide. Papers such as we have had this morning are good examples of what is being done in awakening the obstetric conscience throughout the country. The report of the Association of American Medical Colleges published last year, with an extensive survey under the direction of Dr. Robin Buerki, shows the fine efforts being made in certain places, the desultory efforts in other places, and the absence of all effort in too many localities.

We have come to distinguish between the terms "graduate education" and "postgraduate education" in obstetrics. Graduate education is at the level of graduate study in any other department of the University leading to an advanced degree, while postgraduate education is not of such advanced type, but is intended to keep the medical profession acquainted with the problem of maternal welfare. Dr. Lapham spoke about the great number of physicians that had been taking such courses under various plans. Dr. Buerki's survey emphasized not the number of physicians that were taking these courses but the overwhelming number of physicians that were not taking them.

They found in this survey that the gross results as measured by maternal morbidity and deaths or early deaths of babies are an exact measure of the work that is being done in the localities where these educational plans are being carried out. We have learned from Dr. Williams this morning what the effect of such efforts has been in Philadelphia. That is probably the best example of the seminar method. He claimed no originality but I think they are approaching perfection in developing this method.

We as a Society do not need to worry about advanced graduate education. Medical educators are taking care of that, although they have not reached the limit of the possibilities. In this discussion today, however, we are not considering the training of specialists, but are considering what can be done to keep the medical profession on a high level of practice.

This Society should be the one to encourage this great movement because we represent more states than any other society, 28 of the 48 states. For many years in Iowa, Wisconsin, Minnesota, and other midwestern states we have been undertaking this work. Minnesota had a mortality rate of 6.0 when we began in 1915 to have maternal mortality statistics by the U. S. Census Bureau. The national rate was 7.0 including the southern districts where the negro problem and the economic situations are such great factors. Our maternal mortality rate for the state of Minnesota last year had dropped to below 2.0. The Health Commissioner of Minneapolis told me recently that in the city of Minneapolis where the University is located the maternal mortality is 1.3. Iowa, Wisconsin, and North Dakota together with other states where postgraduate courses are given have the lowest maternal mortality in the United States.

In Minnesota and, I presume, in the other states success has been due to cordial cooperation of the Minnesota State Medical Society, the Minnesota Obstetrical and Gynecological Society, the State Department of Health, the University of Minnesota and the Minnesota Maternal Welfare Committee. These organizations work together and every effort that is made along these lines is done after consultation and with cooperation. For example, our extension courses are given on the University campus in a building built for that purpose and are under the direction of a full-time director of postgraduate medical education of the Medical School. The University faculty with some additions from other members of the State society do the teaching. They are trained teachers, which we think is very essential.

We have tried various methods of sending out teachers to various parts of the state, but now we are conducting all our courses on the campus. Those courses are given two or three times a year on different phases of obstetrics and pediatrics. This movement is so big that the universities will have to organize a new department of postgraduate medical education with a full-time director.

The secret of the whole thing is cooperation of all agencies that may be factors; the state medical society, the local and state obstetric and gynecologic society, the health department, the State university, and the maternal welfare committee. When you get forces like these working together you can lower your mortality as much as 70 per cent, as demonstrated by Dr. Williams in Philadelphia, by Minnesota, Iowa, Connecticut, and in many states where any of these different efforts for postgraduate medical education have been undertaken.

DR. VIRGINIA E. WEBB, NEW ORLEANS, LA.—The papers of Dr. Williams and of Dr. Lapham have both brought out the key point in postgraduate education, that is, the use of actual case histories as the basis for teaching. This type of material cannot fail to interest the men who are actually responsible for the results obtained and the men who are confronted with similar problems in their own practices.

Dr. Williams has pointed out the problems encountered in Pennsylvania in conducting institutes or seminars, in particular the indifference of many members of the society and the difficulty of obtaining suitable teams of speakers to conduct these institutes because of the special ability needed to teach general practitioners. In the type of program which Dr. Lapham has outlined, it is very necessary that the consultants be well chosen in order that they be able to hold the interest of the hospital staffs and visiting physicians.

I would like to emphasize the recommendations which Dr. Lapham has made that the consultants conduct meetings at which obstetric procedures are discussed, morbidities and mortalities are analyzed and pathologic reports presented. It seems to me that the methods which have been used in Philadelphia could be very easily

used as a basis for preparation of reports on maternal mortalities. Every effort should be made to induce willingness on the part of the staff members to discuss frankly the mortalities and morbidities with the consultant acting as an impartial referee.

Dr. Lapham's point with regard to the study program, including pediatric consultation, is well taken. Again, the method of study of stillbirths and neonatal deaths used in Philadelphia might well be worked into the program carried on in the hospitals. In future plans for Louisiana it is anticipated that this will be done.

Recognizing the unusual local situation of having six Charity Hospitals in our State, through which a program of postgraduate education might be conducted, the plan outlined by Dr. Lapham was undertaken. Concrete results as have been pointed out by Dr. Williams are not yet measurable, but it is hoped that within a very few years the program will bear fruit in reducing maternal and infant mortality in the State of Louisiana.

DR. HOWARD H. CUMMINGS, ANN ARBOR, MICH.—Twelve years ago in the State of Michigan, Dr. James Bruce was appointed director of postgraduate medicine of the University of Michigan, and for the past six years I have had the privilege of working with him. I want to report the response of the Michigan physicians to this plan. Our effort is a cooperative one, shared in by the University of Wayne, the University of Michigan, the Michigan State Medical Society, and the Department of Health.

A survey made twenty-five years ago in our state showed that 17 per cent of the doctors of Michigan had taken some postgraduate work throughout their medical career. Last year, using what we call the Michigan plan, over 55 per cent of the doctors of Michigan had taken postgraduate work.

In the fall during the month of October and in the spring during the month of April, these men have the work taken to them. In the lower peninsula they will have to drive not more than fifty miles to get the work, and next year we will open five centers in the northern peninsula. For four days we thus bring to the doctors of our state the progress made in the various fields of medicine and over 2,500 doctors are coming every year to attend these lectures. As far as obstetrics is concerned, we always have an obstetric subject presented in both the fall and spring sessions.

In addition Dr. Norman Miller and Dr. Norman Kretzschmar instruct doctors with large obstetric practices who come to the University and take two weeks refresher courses. We have in Detroit also a course for men who attend the courses in their vicinity.

The work is growing rapidly. We have 4,500 doctors belonging to our State Society and over 55 per cent are taking postgraduate work every year. This must be reflected to the people of Michigan in an improvement not only in obstetric practice but in other medical sciences.

DR. E. D. PLASS, IOWA CITY, IA.—Dr. Litzenberg made a statement which must be challenged to some extent. He said, I believe, that graduate education was on a firm foundation and in no danger. There is one element of danger in the situation with which we should be familiar so we can combat it.

The objective of graduate education in obstetrics and gynecology in this country at present is to qualify young men for the Board examination so they may be given a diploma of the Board. Last spring there developed in the Advisory Committee for Medical Specialties the concept that the training period of these graduate students should be resolved into two equal periods of eighteen months, one interval

given over to a study of the basic sciences and the other eighteen months to clinical instruction. Most of us will agree that basic science instruction is worth while. So also most of us will agree that eighteen months is not a sufficient time to give even a brilliant young man adequate clinical training. Fortunately it was not adopted. Apparently there are certain individuals on the Advisory Committee who are trying to develop graduate education in obstetrics and gynecology just as it is in biology or psychology or some of the other nonmedical disciplines. I think we should be cautious and should discourage any effort to decrease the clinical training of these young men to any such extent. In the final analysis, the objective of the Board, as I see it, is to assure the development of adequately trained clinical obstetricians and gynecologists, so that the women of the country may have better care than they would otherwise have. I believe this trend toward over-emphasis on the basic sciences may defeat that really broad objective.

DR. WENDELL H. STADLE, BATTLE CREEK, MICH.—I would like to talk about the awakening effort in the small town. I am from Battle Creek, Michigan, where we deal with a great many rural cases. The plan we have in conjunction with the Kellogg Foundation is one of the best to improve rural obstetrics I have heard of in a long time. We are interested in the records of all of the four types of cases which Dr. Williams told you about, stillbirths, neonatal deaths, maternal deaths, and deaths of the child occurring one month after delivery. We go so far as to send out into the rural areas a councilor who will go to the family to find out their circumstances, and whether or not there was a reason why the woman was not sent to a hospital. We have gone to the doctor who delivered the woman and questioned him. We have taken all the hospital records, and have brought a report back to the committee of doctors who study the case to determine whether the fault was due to lack of good medical attendance, hospitalization, consultation, nursing care, financial, or social problems, in the same way as is done in the larger cities. We have learned that it is time to go to the man out in the country and to give him every help. You cannot force him to do things, but you can bring to him things that are interesting.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—Many factors tend to better obstetric work which already have been reflected in a lessened morbidity and mortality the country over. Among these is the enormous increase in the use of hospital facilities for parturients, for the hospital obstetric technique is superior to anything which may be employed in the home. The registration of good hospitals by the American Medical Association, and the recognition by the College of Surgeons of those hospitals which have demonstrated peculiar fitness for their work have been invaluable.

In Chicago forty years ago about half of all deliveries were conducted by midwives, while in 1938 only 548 births were managed by midwives. In this same year in Hartford, Conn., 99 per cent of all births were hospital births; in Philadelphia the rate was 84.4 per cent. In 1939 the registered hospitals of the country could have taken care of 74 per cent of all national births if they were fully occupied and with unrecognized hospitals approximately 80 per cent of all births could have been hospitalized. Yet but 48.0 per cent were actually controlled in hospitals.

DR. HIRAM W. KOSTMAYER, NEW ORLEANS, LA.—In the final analysis this question goes back to the character of the doctor, to his interest in the program and to his integrity. If our medical schools through their undergraduate curriculum, their internships and their residencies are turning out a class of men who will not have to be kept educated but will keep themselves educated, perhaps the necessity

for postgraduate or graduate medical training other than leading to the advanced degrees, may in the future become unnecessary.

At present, however, it seems to me of paramount importance to reach the physicians, more particularly perhaps in the rural districts but in many of the urban districts as well. At Tulane we have tried to reach the so-called general practitioners in the rural communities in one of several ways. The two important ones are intramural programs and extramural or extension teaching programs. At each session at Tulane we have in attendance considerably over 200 men and women physicians. They are not confined to the immediate geographic surroundings but come from the four points of the compass of the United States. Finding, however, that there are a good many physicians who either could not or would not come into Tulane for postgraduate medical training we have been conducting for some years our postgraduate extramural training. This has been confined to the southern states but not always to obstetrics and pediatrics.

DR. LAPHAM.—Dr. Williams' paper demonstrated a proved method by which maternal and infant mortality can be decreased. This is probably one of the best long-term maternal programs that has ever been presented, and I hope that everyone here will be stimulated to put into operation such a program if it is not already developed in his community.

Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Thirteenth Annual Meeting, October 2, 3, and 4, 1941

The following papers were presented:

- Clinical Application of Ergonovine During the Third Stage of Labor.** Dr. A. W. Diddle (by invitation), Iowa City, Ia. (For original article, see page 450.)
- Diaphragmatic Hernia in the Newborn Infant.** Drs. John A. Haugen and C. J. Ehrenberg, Minneapolis, Minn. (For original article, see page 502.)
- The Relation of Inhalation Analgesia and Anesthesia to Asphyxia Neonatorum.** Dr. Curtis J. Lund (by invitation), Madison, Wis. (For original article, see page 365.)
- Radium in the Treatment of Uterine Bleeding Caused by Benign Lesions.** Drs. Lawrence M. Randall, Sim B. Lovelady and Fletcher S. Sluder (by invitation), Rochester, Minn. (For original article, see page 377.)
- The Use of Uterine Packs Impregnated with Sulfamilamide.** Drs. Harley E. Anderson, Herman L. Gardner, M. F. Gunderson, and J. M. Slack, Omaha, Nebr. (For original article, see page 410.)
- Syphilis in Obstetrics.** Dr. E. D. Plass, Iowa City, Ia. (For original article, see page 484.)
- Nutritional Edema in Pregnancy.** Dr. R. E. Arnell, and W. F. Guerriero, New Orleans, La. (For original article, see page 467.)
- A Review of Seventy-five Cases of Eclampsia.** Drs. G. S. McClellan, W. D. Strayhorn and P. M. Densen, Nashville, Tenn. (For original article, see page 493.)

- Premature Rupture of the Membranes.** Drs. John H. Morton, C. S. Peabody, John Newdorp, and Fred L. Adair (by invitation), Chicago, Ill. (For original article, see page 422.)
- Gynecographic Aid in the Diagnosis of Ectopic Pregnancy.** Dr. Irving F. Stein, Chicago, Ill. (For original article, see page 400.)
- A Study of One Hundred and Fifteen Cases of Ruptured Ectopic Pregnancy.** Dr. W. O. Johnson, Louisville, Ky. (For original article, see page 437.)
- Nutrition Study in Pregnancy.** Dr. Philip F. Williams, Philadelphia, Pa. Guest speaker.
- Postgraduate Hospital Teaching Program through Consultation Service in Community Hospitals.** Dr. Maxwell E. Lapham (by invitation), New Orleans, La.
- Graduate Education in Obstetrics.** Dr. Philip F. Williams (by invitation), Philadelphia, Pa. (For original article, see page 528.)
- Clinical Evaluation of Equine Gonadotropin.** Dr. Laman A. Gray, Louisville, Ky. (For original article, see page 387.)
- Office Curettage for Prolonged and Resistant Puerperal Bleeding.** Dr. Phil C. Schreier, Memphis, Tenn.
- Complete Laceration of the Perineum and the Repair.** Dr. Joseph W. Kelso, Oklahoma City, Okla.
- Effect of Lymphogranuloma Venereum on Pregnancy, Labor, and the Fetus.** Drs. C. Leon Wilson (by invitation) and H. Close Hesseltine, Chicago, Ill. (For original article, see page 459.)
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CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 17, 1941

The following case reports were presented:

- A Case of Unruptured Tubal Pregnancy Diagnosed by Gynecography.** Dr. Irving F. Stein. (For original article, see page 525.)
- Theca Cell Tumor.** Dr. W. C. Danforth. (For original article, see page 526.)

The following paper was presented:

- Pregnancy in the Syphilitic Mother.** Dr. S. J. Benensohn. (For original article, see page 508.)

Correspondence

Early Ligation of Cord

After reading the editorial by Dr. Harry Bakwin, on "Depriving the Infant of Its Placental Blood," in the October, 1941, issue of the JOURNAL, I would state that I am in accord with its contents. But, I feel that we should not overlook other factors, which might mean either life or death, a normal child or one perhaps showing brain tissue involvement. We should also take into consideration the type of labor, that is, whether or not it has been prolonged, with the head pounded against the perineum, or where there is a hematoma.

In all types of breech delivery and all types of forceps delivery, there is always the danger of a tear in the tentorium cerebelli, and in these instances one would want a decreased amount of fluid in the blood stream.

This specific group of cases should receive further study relative to depriving the infant of some of its placental blood.

Usually, following these particular types of cases, I give from 10 to 20 c.c. of maternal blood, into the gluteal region or under the scapula. It tends to hasten coagulation in the baby's blood, thereby checking any bleeding in that particular region and avoids intercranial pressure which brings about respiratory embarrassment. This is kept up for a period of from three to five days. In this way one can build up the loss of red corpuscles and also the hemoglobin. In many of these cases one notices most particularly respiratory embarrassment due to bleeding in the tentorium cerebelli. Soon after the administration of the blood, this tends to clear up. The same applies to a child that may become spastic after delivery.

A. HERBERT KANTER, M.D.

Columbus, Ohio
December 12, 1941.

To the Editor:

Though late ligation of the cord leads to an increase in the blood volume of the newborn, it is hardly likely that this would affect the bleeding which results from the tearing of tissues. Under such circumstances the use of vitamin K or, better, one of the substitutes, is indicated to bring the coagulability of the blood within the normal range. There is no reason to use blood subcutaneously or intramuscularly, since this does not increase the coagulability of the blood as well as vitamin K; indeed it is doubtful whether it increases it at all. Red blood cells, given parenterally, except by the intraperitoneal route, do not enter the blood stream.

HARRY BAKWIN, M.D.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Toxemia of Pregnancy

Hofbauer, J.: *New Orientation on the Etiology of the Toxemia of Pregnancy*, West. J. Obst. & Gynec. 49: 615, 1941.

The writer presents a succinct account of new concepts regarding the pathogenesis especially of late toxemia, dealing particularly with the biologic significance of three well-defined principles, namely histamine, the posterior pituitary hormone and acetylcholine.

In his opinion, increasing information in regard to interaction of these three pharmacologic agents during pregnancy provides hope for clarification of certain fundamentals in the etiology of toxemia.

From a consideration of the pivotal position of the liver in the detoxification of products of hormonal secretion, in the storage of glycogen, plasma protein, and water metabolism, the view crystallizes that in the prenatal period efforts toward preservation of integrity of liver function as a guard against possible toxemia may be of decisive importance.

HUGO EHRENFEST.

Penfold, W. J.: *On the Nature of Eclampsia*, Med. J. Australia 11: 198, 1941.

The author states that there are signs of acidosis in eclampsia, the specific acid in excess being lactic acid. This probably accounts for the absence of glycogen in the liver. In eclampsia the synthesis of lactic acid to glycogen in the liver is defective. One has to deal with a derangement of the Cori cycle produced by infection or toxemia, so that lactic acid is not promptly and efficiently converted into glycogen. It accumulates in the body and gives the coma of acidosis. The author places great emphasis on infection as a theoretical cause in eclampsia.

The author deems it necessary to make good the defect in the alkali reserve which occurs in eclampsia. The alkali must not be given in excess, since the patient might pass from the convulsions of eclampsia to those of alkalosis. He concludes that eclampsia is an acute sarcolactic acid intoxication occasioned by a large production of the substance within the body, and by an interruption of its disposal by the synthesis of glycogen, which depends upon the presence of some infection.

WILLIAM BERMAN.

Page, E. W.: *Effect of Eclamptic Blood on Urinary Output and Blood Pressure of Human Recipients*, J. Clin. Investigation 17: 207, 1938.

Page undertook to determine whether the transfer of 400 c.c. of blood from patients with severe pre-eclampsia or eclampsia to normal pregnant women would have any effect on the blood pressure, urinary output, and symptomatology of the recipient and to discover in eclamptic blood traces of posterior pituitary in excess

of the amount that might be present in normal blood. Thirty-seven determinations of antidiuretic effects together with blood pressure curves were done on 28 patients. As little as 0.01 unit of solution of posterior pituitary may be readily detected on suitably prepared normal human test subjects. Transfusions of 500 c.c. of blood from normal donors do not result in a significantly altered blood pressure or urinary output in the recipient, although the results suggest the presence of traces of posterior pituitary in normal blood. If small amounts of solution of posterior pituitary are added to human blood in vitro and allowed to stand for from thirty to sixty minutes before transfusion, a definite antidiuretic response may be obtained in the recipient. If large amounts of solution of posterior pituitary are given to donors prior to the withdrawal of blood, no definite antidiuretic response can be obtained in the recipient, indicating a rapid elimination or destruction of the hormone from the circulating blood stream. When amounts of 400 c.c. of blood are rapidly transferred from patients with eclampsia or severe pre-eclampsia to normal pregnant women, the recipients do not show any rise in blood pressure, interference with diuresis or untoward symptoms. The results do not confirm the contention that there is a toxic substance in toxemic blood or support the theory that there is a hypersecretion of the posterior pituitary in eclampsia.

J. P. GREENHILL.

Yamada, K.: A Study of the Relationship Between the Origin of Eclampsia and Allergy, Japanese J. Obst. & Gynec. 23: 2, 1940.

Yamada experimenting with rabbits found histologic differences in the pregnant animals which were sensitized to blood serum from eclamptic women but were not present in the animals sensitized to blood serum from noneclamptic women. This he attributes to allergy. Furthermore, he found that an antigen which produced a strong shock reaction was to be found only in the blood serum and placentas of eclamptic patients. The author, therefore, firmly believes that eclampsia has its origin in allergic changes.

J. P. GREENHILL.

Cope, Cuthbert Leslie: Excretion of Pregnanediol in Toxemia of Pregnancy, The Lancet 2: 158, 1940.

Previously published reports have indicated a greatly reduced excretion of pregnanediol glucuronidate in the urine of patients with toxemia of pregnancy. A study by the author of a series of ten cases of toxemia does not confirm this claim. During the last month of normal pregnancy, 30 to 90 mg. of pregnanediol glucuronidate is excreted daily with a mean figure of 55 mg. In the toxemic group the excretion varied from 28 to 55 with a mean of 39.4 mg. In one pregnant patient with chronic nephritis no pregnanediol was excreted.

CARL P. HUBER.

Ch'ing-shan, Lu: Total 24-Hour Urinary Excretion of Estrogens in Normal and Toxemic Pregnancies, Chinese M. J. 59: 131, 1941.

The daily urinary excretion of estrogens was studied in normal pregnancies as well as in cases of pre-eclampsia, eclampsia, chronic nephritis, mild toxemia, and vomiting of pregnancy.

Except in cases of hyperemesis, a decrease in the excretion of estrogens in the urine was found in all the toxemic pregnancies.

A lowering of the urinary estrogen was also observed in a patient receiving corpus luteum during pregnancy.

C. O. MALAND.

Peckham, Charles H.: The Effect of Syphilis and Its Treatment on the Incidence of Toxemia of Pregnancy, *Am. J. Syph., Gonorr. & Ven. Dis.* 25: 280, 1941.

This is a report of 13,742 consecutive deliveries at the Johns Hopkins Hospital. Antisyphilitic treatment administered to pregnant syphilitic women during pregnancy does not increase the incidence of toxemias of pregnancy.

C. O. MALAND.

Setzer, O.: Dependency of Eclampsia Upon Climatic Factors, *Zentralbl. f. Gynäk.* 64: 972, 1940.

The author studied meteorologic conditions obtaining during 129 attacks of eclampsia. A change in weather either to colder or warmer was noted at the onset of 75 per cent of cases. A change to cold was found in 54 per cent more cases than a change to warm weather. Relative humidity was high at the onset of eclampsia in 68 per cent of cases. An increase in the incidence of eclampsia was found in April, May, and June and in the months in which there were many changes from cold to warm weather. Barometric pressure as a factor was not considered in this study.

R. J. WEISSMAN.

Lennon, G. Gordon: Eclampsia—A Statistical Review, *Brit. M. J.* 1: 944, 1938.

A comprehensive study and report of eclampsia in the northeastern area of Scotland is given. Colon lavage, gastric lavage, and venesection (for blood pressure over 160 mm. Hg) are done. Also 1 gr. of thyroid extract is given daily to further diuresis. Occasionally, veratrine, $\frac{1}{2}$ c.c. intramuscularly, is used as an alternative for venesection. Membranes are ruptured for labor induction if the patient is at or near term. When labor has already begun, it is terminated as quickly as possible. Conservative measures are employed only if the patient is unduly far from term and if she responds well to treatment.

The incidence of eclampsia in the Aberdeen Hospital over a period of five years was 1.59 per cent. The incidence was 18 per cent higher in the winter months from October to March than from April to September; 73.77 per cent of the cases occurred in either first or second pregnancies, 65 per cent up to the age of 30 years without any deaths. The mortality rate over 30 years was 28.6 per cent. Antipartum eclampsia was as common after 30 years of age as before. However, the post-partum type was more common (77 per cent of cases) before the age of 30. There was a striking difference between the mortality rates for towns (5.71 per cent) and for the county (15.4 per cent).

The maternal mortality rate for this series was 9.84 per cent. This figure was doubled in illegitimate pregnancies. The fetal mortality rate, including neonatal loss, was 39.34 per cent.

F. L. ADAIR AND JOHN A. HAUGEN.

McKelvey, John L.: Remote Vascular Lesions of the Toxemias of Pregnancy and Their Clinical Significance, *The Journal Lancet* 51: 35, 1941.

The author gives consideration to the role of pregnancy in the production of arteriosclerosis and points out that pregnancy always advances the lesion. In some cases pregnancy may produce a speedy progression of the disease with ultimate destruction. Of all the known exacerbating agents in hypertension, pregnancy is the most certain and severe. Not only does the pregnancy affect the arteriosclerosis but the pregnancy may be prejudiced by the toxemia, the major effect lying in the production of the condition known as ablatio placentae. It is felt that the

persistence of a systolic blood pressure of 140 mm. of mercury and/or a diastolic pressure of 90 mm., and/or albuminuria allows a diagnosis of arteriosclerosis. Whether the hypertension is primary or secondary to the toxemia is only of academic interest. It is stated that at the Johns Hopkins Hospital in a ten-year period following a diagnosis of arteriosclerotic toxemia, 25 per cent of the patients died. It is the author's opinion that if early recognition of the lesion and appropriate sterilization were carried out, the dreadful remote mortality of the disease might be somewhat lessened.

WILLIAM BERMAN.

Heynemann, Th.: Eclampsia and Its Precedent Conditions, *Deutsche med. Wehnschr.* 66: 757, 1940.

Heynemann believes that there is a storage of metabolic products in the placenta which affects the gravida in eclampsia and its related states. Early diagnosis and treatment are essential as the prognosis is seven times better in the pre-eclamptic states. An albumin-, fat-, and salt-poor diet with 1 liter of fluid intake is recommended. Prophylactically a diet is given in which vegetables and fruits largely replace meats and fats. Patients are hospitalized as soon as definite indication of disease appears. In considering increase of blood pressure, the individual's usual pressure should be considered rather than the reading per se. Diagnostic helps in experienced hands are: (1) Reduction of the response to galvanic stimulation of the median nerve. Alterations in the response have prognostic value; (2) Retinal vascular spasm; (3) Alterations of capillary flow as noted in nail folds. Venesection for control of hypertension should be carefully controlled by constant blood pressure readings to avoid collapse.

R. J. WEISSMAN.

McNeile, Lyle G., and Page, Ernest W.: The Personality Type of Patients with Toxemias of Late Pregnancy, *Am. J. M. Sc.* 197: 393, 1939.

A method used by a previous worker in the study of nonpregnant individuals with essential hypertension has been utilized to study the personality types of women with normal pregnancies, and with pregnancies complicated by pre-eclamptic toxemia, eclampsia, glomerulonephritis, or essential hypertension.

The results indicate that only those women with essential arteriolar hypertension (as a group) differ significantly from the normal in having personalities characterized by an increased psychomotor activity.

Further correlations are shown between the diagnosis and the age, parity, height, weight gain with pregnancy, and family history. A classification based on the probable origin of the hypertension is suggested for use.

The relationship between the hypertensive personality and the late toxemias of pregnancy with its value in differential diagnosis is discussed.

J. THORNWELL WITHERSPOON.

Sakler, B. R.: Eye Changes in Pregnancy, *Ohio State M. J.* 36: 522, 1940.

The ophthalmoscope should be considered a valuable adjunct in the modern management of the toxemias of pregnancy because hypertensive, angiospastic, toxemic, retinal changes appear early. It is generally conceded that toxemic cases with normal ocular fundi make a complete recovery. The visual prognosis in toxemic patients who develop peripheral retinal changes is on the whole surprisingly good. A diagnosis of optic neuritis, retinitis, or retinal detachment, presents a definite indication for the immediate termination of the pregnancy, in an effort to safeguard the future health and vision of the mother.

J. P. GREENHILL.

Irving, F. C.: A Study of Five Hundred Consecutive Cases of Pre-eclampsia, *Canad. M. A. J.* 137: 40, 1939.

The author summarizes 500 cases of pre-eclampsia seen in a two-year period at the Boston Lying-in Hospital. Of these 397 were mild with hypertension of mild degree and no more than a slight trace of albumin in the urine, 248 were primiparas and 27.8 per cent of the multiparas had had pre-eclampsia in a previous pregnancy.

The leading signs and symptoms were edema in 71.6 per cent, headache in 41.8 per cent, vomiting in 27.45 per cent, and visual disturbances in 27.0 per cent. Blood chemistry studies were of little clinical value. Patients with a systolic blood pressure above 150 or a diastolic pressure above 100 were hospitalized.

Treatment consisted of bed rest, restriction of the fluid intake below the output of the preceding twenty-four hours. A milk diet of 1,200 c.c. or less was given for the first three days followed by a low salt, low protein diet of 1,378 calories. Magnesium sulfate was given for catharsis.

Of the pregnancies, 39 per cent were terminated artificially, 8 per cent by cesarean section, but only 8 of the 40 cesarean sections were performed because of the toxemia. The fetal mortality was 2.6 per cent in 194 pregnancies terminated between thirty-two and thirty-six weeks, and 5.9 per cent in 252 patients delivered at from thirty-six to forty weeks of gestation. The gross fetal mortality was 6.9 per cent for the group, which is only 0.6 per cent greater than for the hospital population during the same period.

Five patients developed convulsions, all post partum. There was one maternal death following low segment cesarean section performed because of a contracted pelvis after twenty-four hours of trial labor. Death was due to general peritonitis. The maternal mortality was 0.2 per cent.

CARL P. HUBER.

Furtado, Alfonso H.: The Treatment of Eclampsia by the Method of Stroganoff, *Rev. de gynec. e d'obst.* (Rio de Janeiro) 2: 386, 1938.

The author, reviewing in detail and recommending Stroganoff's method and statistics, reports a series of 15 cases; 11 of the patients were treated conservatively with no mortality, while in those treated surgically the maternal mortality rate was 8.3 per cent.

MARIO A. CASTALLO.

Guerriero, Wm., Leidenheimer, Henry, and Zander, Edwin: An Analysis of 220 Cases of Eclampsia from Charity Hospital at New Orleans, *New Orleans M. & S. J.* 94: 68, 1941.

The authors base their conclusions upon 220 cases with a fetal mortality of 41 per cent and a maternal mortality of 8.6 per cent. The management of eclampsia involves three considerations: (1) its prevention by adequate prenatal care; (2) the termination of pregnancy if pre-eclampsia cannot be controlled; (3) if eclampsia has definitely set in it should be treated primarily, with delivery delayed until the convulsions have been controlled. Toward the end of the period covered in this study, the incidence of eclampsia and the mortality rate decreased due to better prenatal care. Cesarean section was never performed with eclampsia as the indication per se.

EUGENE S. AUER.

Naeslund, John: Hyperemesis Gravidarum, *Upsala läkaref. förh.* 45: 285, 1939.

Although 62 per cent of the pregnant women attending the author's clinic during 1937 and 1938 suffered vomiting, only 0.6 per cent of that total attendance fell

in the hyperemesis gravidarum group. He briefly reviews the various theories of the causation of hyperemesis.

He develops a theory of the cause of pregnancy toxæmia, particularly in relationship to hyperemesis and abruptio placentæ, which is dependent on the assumption that substances from the ovum enter the mother's blood stream and produce a condition of allergy. The significance of the paternal contribution to the ovum in this connection is emphasized. The author then turns specifically to the blood. The results of investigating the blood groupings in 236 mothers and children and some fathers in relation to nausea, vomiting, and albuminuria of pregnancy indicate that the serious cases are strikingly more numerous when the mother and child differ in blood grouping. Evidence is offered of the presence of fetal blood in the maternal circulation. Allergy studies by the method of intracutaneous injection are described in detail and lead to the conclusion "that substances are sometimes to be found in the body of the pregnant woman which react to injections of blood from the fetus or the father."

A number of histories are reviewed of patients in whom relief was obtained after all other methods had failed, by the use of repeated intramuscular injections of from 1 c.c. to 20 c.c. of the husband's blood.

CLAUDE J. EHRENBURG.

Brandstrup, Ebbe: Some Problems Concerning the Pathogenesis and Treatment of Hyperemesis Gravidarum, *Acta obst. et gynec. Scandinav.* 19: 376, 1939.

In Denmark, hyperemesis each year costs the lives of six women, necessitates 30 to 40 therapeutic abortions, and causes illness and serious inconvenience in over 4,000 women. Treatment with large doses of suprarenal cortex was tried in 11 cases of hyperemesis. In four of the cases the condition was aggravated, necessitating therapeutic abortion, while improvement was seen in the remaining cases. Hence it appears that suprarenal cortex is not a specific remedy for hyperemesis, and the author's results speak strongly against the hypothesis that insufficiency of the suprarenal cortex might be the primary cause of hyperemesis.

The author assumes that hyperemesis is brought about by an abnormal reaction of the organism to the greatly increased hormone production that is a normal feature of pregnancy.

Secondarily, the development of hyperemesis is largely dependent upon psychic factors. As the third factor in the pathogenesis a state of inanition develops, in which severe damage to the liver and the central nervous system is due to a rapid fall in glycogen and to vitamin deficiency, probably caused by the inanition under the special hormonal conditions present in the pregnant organism. In keeping with this view of the pathogenesis, the proper conservative treatment will consist in a sedative, psychic, and restorative therapy aimed to counteract the vomiting and its consequences. Restorative therapy consists in administration of sodium chloride, water, glucose, insulin, and vitamins. The future will show whether suprarenal cortex is to be established as an effective remedy in the restorative therapy. If conservative treatment fails, interruption of the pregnancy is necessary.

J. P. GREENHILL.

Walther, P.: The Treatment of Gastric Pain and Vomiting of Pregnancy by Means of Histidine, *Bull. Soc. d'obst. et de gynéc.* 27: 190, 1938.

Walther used a 4 per cent solution of the monochloride of histidine in 50 cases for nausea and vomiting of pregnancy, and heartburn. Injections are given every day or every second day depending upon the severity of the symptoms. There

are no general reactions from this therapy and only a slight burning sensation locally. The author warmly recommends this medication because he has obtained spectacular results with it.

J. P. GREENHILL.

Westman, A.: *Hyperemesis Gravidarum*, Acta. obst. & gynec. Scandinav. 20: 203, 1940.

In a period of three years, 66 cases of hyperemesis were observed at the Lund Women's Clinic. The treatment generally adopted consisted of abstinence from food, injections of glucose and insulin for one or two days and then an abundant supply of salt by mouth. In 28 women prolan determinations of the urine were made and an increase was found in the majority of the cases. However, there was no parallelism between the severity of the disease and the increase in the amount of prolan. Abortions were induced in the severe cases.

In the discussion of this paper, Ahlstrom said that in his entire career, which included observation of 56 cases of hyperemesis, he had never performed an abortion nor had he observed a death from hyperemesis. He has treated all his cases by psychotherapy with the aid of bromides.

J. P. GREENHILL.

Items

American Congress on Obstetrics and Gynecology

St. Louis, Missouri, April 6 to 10, 1942

The general features of the program for the coming Congress may be announced as follows:

The morning sessions will be divided into two periods from 9:30 to 11 and 11 to 12. The more formal presentations will appear in the first period.

Monday morning at 11 o'clock there will be a general "Obstetric Information Please," based on the well-known quiz program and presided over by a moderator and four experts. This will be repeated on Wednesday morning, for shock and hemorrhage, and Friday, on economics. Clinical conferences on genital infections will be held Tuesday morning at 11 and Thursday morning on "How Not to Treat Carcinoma." During the afternoons various groups will present formal programs devoted to nursing, public health, and hospital administration, among which will be certain combined programs.

A special feature of this Congress will be a daily consultation service at 3:30. About 50 nationally known physicians will make themselves available for fifteen-minute consultations through a registration system by individual practitioners who may desire such advice in their specific problems.

Round table discussions will also be arranged by the section chairmen.

Practical demonstrations are scheduled in the scientific exhibit area on manikin deliveries, home care technique, and blood transfusions. Details of programs of other sections will appear shortly.

Further information is available at the Central Office of the Congress at 650 Rush Street, Chicago. Hotel reservations should be made directly and at an early date. Physicians, nurses, public health administrators, educators, and hospital administrators are urged to send in their registration fee of \$5.00.

Postgraduate Courses in Obstetrics at Chicago Lying-in Hospital

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of \$25.00 is required on registration, \$10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

The general oral and pathologic examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Wednesday, June 3, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Erratum

In the article by Z. J. R. Hollenbeck and P. J. Reel entitled "The Use of Stilbestrol in the Management of the Menopause," page 332, February issue, the cuts are incorrectly placed. Fig. 1 has the caption for Fig. 2, and vice versa.

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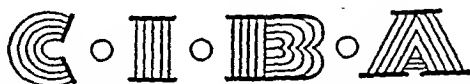
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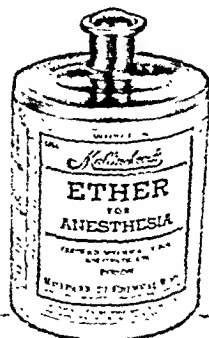
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Original Communications

THE TREATMENT OF TETANY IN PREGNANCY

WITH A BRIEF REVIEW OF THE LITERATURE

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WE CONSULTED the literature when we were confronted with the management of cases of hypoparathyroidism associated with pregnancy. Earlier discussions of the subject were confusing, in fact many of the cases reported simulated toxemias of pregnancy, particularly eclampsia.

One of the best sources of information was that of Kehrer's¹ report written in 1913. He reviewed all of the cases (inclusive) of that year and discussed very completely the subject of tetany in pregnancy. No similar review has been written in the American literature, although the subject of the parathyroid glands has been thoroughly discussed by Thomson and Collip,² Boothby and Davis,³ and Barr.⁴ These authors, however, had very little data on tetany associated with pregnancy. Pool,⁵ in 1917, published an excellent discussion of the female genital apparatus in relation to the parathyroid glands. In this paper a case of postoperative tetany associated with pregnancy was presented.

In a recent paper, Schwartz, Lichtenstein and Curtis⁶ reported a case of postoperative hypoparathyroidism associated with pregnancy successfully treated with dihydrotachysterol (A. T. 10). Because of the infrequency of similar reports and the splendid results obtained with dihydrotachysterol, a summary of previous findings was included in this study.

We wish to report three cases of this type and also to review briefly the literature and to point out some of the altered clinical features of parathyroid insufficiency associated with pregnancy.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

REVIEW OF THE LITERATURE

The subject of tetany is a vast one, hence this review is limited to the specific topic of tetany associated with pregnancy. Complete reviews may be found by Boothby,⁷ Boothby and Davis,³ Barr,⁴ and Thomson and Collip.²

Steinheim,⁸ in 1830, described a form of tetany associated with pregnancy and lactation, and one year later a similar case was described by Dance.⁹ Trousseau,¹⁰ in 1854, considered lactation tetany as the most common form of tetany and proposed the term, "rheumatic contractures of nursing women." A few scattered case reports^{11, 12} appeared during the next few years, but writers who reviewed these cases in later years felt that eclampsia may have been confused with tetany, as we differentiate the two distinct entities today.

With the advent of the first thyroidectomy performed by Koehér,¹³ in 1878, a new etiologic factor for hypoparathyroidism developed. It was not until 1880 that the parathyroid glands were described by Sandström.¹⁴ Weiss,¹⁵ working in Billroth's Clinic, was the first to recognize that tetany might follow thyroidectomy. Gley¹⁶ demonstrated that thyroidectomies would be fatal if the parathyroid glands were also extirpated. These facts were confirmed by Vassale and Generali¹⁷ in 1896.

In Tables I, II, and III we have summarized in chronological sequence, the types of tetany observed and the treatment administered by previous investigators.

The early experimental work of Frommer,²⁰ Halsted,²¹ Massaglia,²² and Thaler and Adler²³ aided in explaining the predisposition of pregnant women in developing tetany. These experimenters showed that in dogs which had survived partial parathyroidectomy for as long as eighteen months the occurrence of pregnancy would precipitate tetany.

Erdheim,²⁴ working with rats in which he had extirpated the parathyroid glands, observed that toward the end of each of two successive pregnancies definite signs of tetany developed. In both instances parturition resulted in complete relief of symptoms.

MaeCallum and Voegtlin²⁶ demonstrated the relationship between the parathyroid glands and calcium metabolism in 1911 and also the relationship between nervous manifestations following parathyroidectomy and the level of the serum calcium.

Werelius,²⁸ in 1913, demonstrated that thyroparathyroidectomized dogs had convulsions in the later stages of pregnancy and often died. He also felt that the fetal parathyroids did not compensate for the absence of the mother's glands.

In demonstration of the variations of experimental animals to hypoparathyroidism associated with pregnancy, the work of Carlson,²⁹ in 1913, was interesting. Carlson²⁹ found that cats submitted to hypoparathyroidectomy in late pregnancy did not have an acceleration or intensification of the symptoms of parathyroid tetany. In dogs subjected to the same procedure, however, 50 per cent died in acute tetany within twelve to twenty-four hours after parathyroidectomy. Carlson²⁹ also found that active immunity was decreased in dogs with parathyroid tetany.

Perhaps the most elaborate discussion of tetany in pregnancy was written by Kehrer¹ in 1913. In his monograph Kehrer¹ reviewed 103 cases in the previous literature to which he added 5 cases of his own.

We have tabulated the types of cases reviewed by Kehrer in Table I. Arbitrarily the year 1913 is used as a dividing line for the data summarized in Tables I and II as "early" and "more recent" literature, respectively.

TABLE I. SUMMARY OF EARLY LITERATURE (1830-1913)

AUTHOR	YEAR	TYPE OF TETANY	TREATMENT AND REMARKS
Steinheim ⁸	1830	Lactation (1 case)	Developed in women while nursing their babies.
Dance ⁹	1831	Lactation (1 case)	Similar to case described by Steinheim. ⁸
Trousseau ¹⁰	1854	Lactation (40 cases)	Described as the "rheumatic contractures of nursing women."
Meinert ¹⁸	1887	Idiopathic (2 cases)	Reviewed 9 cases of idiopathic tetany occurring during pregnancy and added 2 cases of his own. Treatment: poultices, inunctions, baths were used without success. Venesection, potassium bromide, and chloral hydrate were of value. Many of the babies were stillborn. Induction of labor was recommended.
Thomas ¹⁹	1895	Idiopathic (1 case)	Reviewed previous literature. Described a case in a woman of tetany of 12 years' duration, recurring during 6 different pregnancies. Menstruation would precipitate attacks also.
Frankl-Hochwart ²⁵	1907	Idiopathic (10 cases)	Reviewed 51 cases in the literature and added 10 cases of his own. Thirty-eight cases were in post-partum period and 23 cases occurred during the gestation.
McCarrison ²⁷	1911	Thyroid disease associated with tetany (60 cases)	Occurred in women living in goiter regions in India. Observed family tendency and seasonal tetany. Treatment: calomel, rhubarb, and thymol in 5-grain doses twice daily for 2 weeks.
V. Beck ³²	1912	Postoperative	Twenty-five-year-old female developed tetany following thyroidectomy in her third pregnancy. Tetany became worse even with parathyroid implantation and also oral parathyroid gland. Premature induction of labor. Baby died. Therapeutic abortion in following 2 pregnancies.
Kehrer ¹	1913	Complete review I Tetany during pregnancy (30 cases) II Recurring tetany (29 cases) III Postoperative tetany (9 cases) IV Tetany during delivery (3 cases) V Puerperal and lactation tetany (37 cases)	A complete review of the previous cases in the literature (103 cases plus 5 of Kehrer's cases). Used calcium orally for first time (6 Gm. daily). Sodium carbonate given intravenously. Advised placing patients on milk diet. Venesection suggested in some cases. Did not feel that induction of premature labor or therapeutic abortion was necessary. Advised use of thyroid extract in combination with calcium therapy.

TABLE II. SUMMARY OF LITERATURE IN RECENT YEARS (1913-1941)

AUTHOR	YEAR	TYPE OF TETANY	BLOOD CHEMISTRY		TREATMENT AND REMARKS
			CALCIUM	PHOSPHORUS	
Marek ³⁷	1914	Idiopathic (9 cases)	No values	No values	Observed 9 cases including one fatal case Treatment: calcium chloride by mouth and parathyroid extract
Stein ³⁸	1916	Tetany during delivery (1 case)	No values	No values	Inadequate observations. Cases occurred during delivery
Pool ⁵	1917	Postoperative (1 case)	No values	No values	Twenty-seven-year-old white female developed tetany following thyroidectomy. Immediately treated with calcium lactate and transplantation of parathyroid tissue. Went through two pregnancies, developing tetany each time
Roth ³³	1920	Idiopathic (1 case)	No values	No values	Thirty-two-year-old female developed tetany in sixth month of pregnancy. Given intravenous calcium and parathyroid transplantation performed with excellent results (first successful transplantation in pregnancy tetany)
Borchers ³⁹	1920	Postoperative (1 case)	No values	No values	Postoperative tetany which recurred during pregnancy necessitating premature induction of labor
Stenvers ⁴⁰	1922	Postoperative (1 case)	No values	No values	Developed tetany after thyroidectomy. Parathyroid transplantation performed and woman passed through normal pregnancy
Niederche ⁴¹	1923	Idiopathic (1 case)	No values	No values	Treated successfully with oral and intravenous calcium
Krishnamurthy ⁴²	1924	Idiopathic (9 cases)	No values	No values	Observed 9 cases with details of one case in a 20-year-old Hindu female. Developed severe tetany; treated with adrenalin successfully; viable child
Lisser, Smith and Shepardson ⁴³	1927	Tetany during delivery	7.5 mg.	No values	Developed tetany following cesarean section for placenta previa with 1,500 c.c. blood loss. Treated with para-thor-mone successfully
Putz ⁴⁴	1929	Idiopathic (1 case)	No values	No values	31-year-old para v developed tetany; progressively became worse. Died. Post mortem ruled out eclampsia
Wertheimann ⁴⁵	1929	Idiopathic (1 case)	3.1 mg.	No values	Treated with para-thor-mone unsuccessfully and ended fatally

TABLE II—CONT'D

AUTHOR	YEAR	TYPE OF TETANY	BLOOD CHEMISTRY		TREATMENT AND REMARKS
			CALCIUM	PHOSPHORUS	
King ⁴⁶	1930	Calcium intake (1 case)	4.7 mg.	6.7 mg.	Chinese female; due to low calcium intake Treatment: calcium lactate (4 Gm. daily), cod-liver oil (24 c.c. daily). Advised induction of labor
Richardson ⁴⁷	1931	Idiopathic (1 case)	No values	No values	Indefinite report. Treatment with viosterol and calcium successful
Hoxie ⁴⁸	1932	Post partum (1 case)	9.5 mg.	No values	Thirty-four-year-old female developed tetany after delivery. Became worse with each menstrual period. Induced menopause with x-ray and radium without beneficial results
Klaften ⁴⁹	1933	Postoperative (1 case) Hyperventilation (4 cases)	No values	No values	Describes hyperventilation tetany. One case postoperative type. Advises induction of labor and posterior pituitary extract
Pollak ³⁰	1934	Idiopathic (8 cases)	No values	No values	Reported 7 of 8 cases with successful termination. Last case defied treatment including transplantation. Therapeutic abortion performed followed by sterilization
Wester-mann ⁵⁰	1934	Postoperative (2 cases)	4.9 mg.	No values	After thyroidectomy patient went through two pregnancies, having tetanic symptoms controlled by calcium and para-thor-mone
Maxwell ⁵¹	1934	Calcium diets (3 cases)	3.6 mg. 7.7 mg. 4.6 mg.	3.8 mg. 2.2 mg. 3.1 mg.	Chinese women with daily intake of calcium 0.07 Gm. Developed tetany during pregnancy. Para-thor-mone not effective. Vitamin D and sunlight were most effective
Konikow ⁵²	1935	Idiopathic (1 case)	No values	No values	Para i developed tetany in eighth month of pregnancy. Calcium and para-thor-mone gave relief. Normal baby
Swinton and Claiborne ⁵³	1936	Postoperative (2 cases)	No values	No values	First patient had 3 years of tetany following surgery. Normal pregnancy. Second patient had temporary tetany following surgery, then absence of symptoms for 4 years, recurring during pregnancy. Controlled with calcium
Baumgartner and Cowles ⁵⁴	1937	Postoperative (1 case)	6 mg.	6.2 mg.	Seven months after thyroidectomy patient became pregnant and developed tetany. Para-thor-mone, calcium lactate (10-20 Gm. daily) and cod-liver oil (4 c.c. daily)

TABLE II—CONT'D

AUTHOR	YEAR	TYPE OF TETANY	BLOOD CHEMISTRY		TREATMENT AND REMARKS
			CALCIUM	PHOSPHORUS	
Klatskin ⁵⁵	1938	Post partum (1 case)	7.1 mg.	5.6 mg.	Para iii. Developed tetany on seventh post-partum day. Calcium lactate and cod-liver oil
Hoesch ⁵⁶	1938	Postoperative (1 case)	No values	No values	Postoperative female developed tetany in fourth month of pregnancy. Normal delivery. Treatment: bed rest
Risak ⁵⁷	1938	Idiopathic (1 case)	10 mg.	3.3 mg.	19-year-old white female with constitutional background for tetany
Anderson and Lyall ⁵⁸	1939	Postoperative (1 case)	5.5 mg.	No values	Postoperative tetany in 38-year-old female. One year later became pregnant. Developed tetany in 3 successive pregnancies. Calcium therapy
Verhage ⁵⁹	1939	Postoperative (1 case) Idiopathic (1 case)	Low values	No values	Developed symptoms during pregnancies. Treated with parathormone
Liu et al. ⁶⁰	1941	Osteomalacia and tetany due to low calcium intake (4 cases)	No values	No values	These patients had history of tetany and osteomalacia associated with pregnancy due to dietary deficiency. Vitamin D and calcium gave immediate relief

In Henke and Lubarsch's *Handbook of Pathology*,³¹ Herxheimer has an excellent discussion of the parathyroid glands. Very little information relative to tetany and pregnancy was available in this monograph. About 20 cases of transplantation of the parathyroid glands had been performed inclusive of the year 1922 with about 50 per cent good results. Although this type of procedure had been done as early as 1912 by V. Beck,³² it was not until 1920 that a successful result was obtained in a case of maternal tetany.³³

With the discovery of dihydrotachysterol (A. T. 10) by Holtz,³⁴ in 1933, a new therapeutic aid offered possibilities for excellent results in cases of maternal tetany. In 1934, Holtz³⁵ reported the results of the treatment in a case of delayed lactation tetany with A. T. 10. This case was one of Hahn's cases in the Berlin Charite Hospital. Holtz and Rossman,³⁶ in 1938, reported on three cases of "maternal tetany" treated with dihydrotachysterol (A. T. 10). In Table III we have summarized 9 cases treated with A. T. 10 reported in the previous literature.

Our review is not entirely complete, particularly of isolated case reports in the European literature, because of difficulties in obtaining these reports at present.

TABLE III. SUMMARY OF CASES OF PREGNANCY TETANY TREATED WITH DIHYDROTACHYSTEROL

AUTHOR	YEAR	TYPE OF TETANY	BLOOD CHEMISTRY		TREATMENT AND REMARKS
			CALCIUM	PHOSPHORUS	
Hahn quoted by Holtz ³⁴	1934	Lactation (1 case)	No values	No values	Hahn of the Charite Clinic in Berlin observed a case of delayed lactation tetany treated with dihydrotachysterol
Arnold, Holtz and Marx ⁶¹	1936	Postoperative (1 case)	No values	No values	Following thyroidectomy developed tetany with psychic changes and bilateral cataracts. Cataract operation performed. Became pregnant; placed on A.T. 10 which had to be increased in fourth month. Baby normal
Holtz and Rossman ³⁶	1938	Postoperative (2 cases) Idiopathic (1 case)	5.5 mg.	No value	First case: 22-year-old white female. Postoperative type developed severe symptoms in fourth month. Began A.T. 10 1.5 to 3 c.c. weekly, increasing dosage until 3 c.c. daily were used. Discontinued during labor which was premature. Thyroid had also been prescribed. Second pregnancy also successful with dihydrotachysterol therapy
			7.8 mg.	No value	Second case: Idiopathic. Began therapy with 10 c.c. initial dose of A.T. 10, increasing from 1 c.c. until 3 c.c. daily. Lowered to ½ c.c. daily as delivery approached
			7 mg.	No value	Third case: Treatment started with 5 to 8 c.c. A.T. 10 weekly; gradually increasing to 3 c.c. daily
Franco ⁶²	1940	Idiopathic (1 case)	5 mg.	10 mg.	All four children of these three mothers were normal Female, 15 years old, developed tetany with onset of menses. Controlled on parathormone, calcium, viosterol. At 23 years of age became pregnant and improved. Given A.T. 10 following pregnancy. 1.5 to 3 c.c. had been used during menstrual periods
Kowallis ⁶³	1941	Post partum (1 case)	5.1 mg.	4.8 mg.	Developed tetany in sixth postpartum week. Treated with large doses of calcium lactate and A.T. 10
Weber and Richardson ⁶⁴	1941	Postoperative (1 case)	6.3 mg.	5.9 mg.	Developed pre-eclampsia and induction of labor at seventh month. Treated with calcium lactate and A.T. 10
Schwartz, Curtis and Litchensteins ⁶	1941	Postoperative (1 case)	4.8 mg.	5.8 mg.	Treatment with 1 c.c. A.T. 10, calcium lactate and viosterol in first 5 months of pregnancy. A.T. 10 increased to 3 c.c. daily in last 4 months. Normal baby. Pomeroy sterilization done following pregnancy

ETIOLOGY, CLINICAL FEATURES, AND DIAGNOSIS

The classification of the various types of tetany has been attempted by Ellsworth⁶⁵ and Albright and his co-workers.⁶⁶ Arbitrarily we have in Tables I to IV classified the cases in the literature as maternal or pregnancy tetany to distinguish them from cases of tetany occurring in males and nonpregnant females. In Table IV, several types of tetany, associated with pregnancy previously described in the literature, are tabulated.

TABLE IV. CLASSIFICATION AND SUMMARY OF TYPES OF TETANY IN PREGNANCY

Type 1. Postoperative		26 cases
2. Idiopathic or spontaneous		145 cases
a. During pregnancy	95 cases	
b. During delivery	5 cases	
1. Due to blood loss	1 case	
(Described by Lissner et al. ⁴³)		
2. Hyperventilation tetany	4 cases	
(Described by Klawns ⁴⁹)		
c. Post-partum, puerperal, and lactation types	41 cases	
(Note: Difficult to differentiate these cases, hence all grouped together.)		
3. Tetany due to low calcium intake or vitamin D deficiency		9 cases
(Described by Maxwell, ⁵¹ King, ⁴⁶ Liu et al. ⁶⁰)		
4. Thyroid disease associated with pregnancy		60 cases
(Described by McCarrison ²⁷)		
Total		240 cases

The first type, postoperative hypoparathyroidism, may be either temporary or permanent following thyroidectomy. A disturbance of the blood supply or trauma to the parathyroid glands may cause only temporary symptoms, while complete removal would produce permanent symptoms.

The remaining types listed in Table IV cannot be clearly defined. Perhaps the term spontaneous or "idiopathic" would be satisfactory for the entire group, because a definite etiologic agent is often lacking.

The incidence of the various types of tetany in pregnancy is not very well established. Early figures, such as those of Niederehe,⁶⁷ Adler and Thaler,²³ record maternal tetany as 3 per 10,000 births.

The presence of the postoperative type is dependent upon the number of thyroidectomies. Swinton⁶⁸ of the Lahey Clinic reported an incidence of 0.2 per cent in 13,000 thyroidectomies developing tetany following surgery. McCullagh⁶⁹ (Cleveland Clinic) had a 1.3 per cent incidence in a series of 11,508 thyroid operations, and a figure of 1.5 per cent was reported by Boothby, Haines and Pemberton⁷⁰ of the Mayo Clinic. The number of these patients, however, who are in the childbearing age and become pregnant are relatively infrequent.

The diagnosis of tetany associated with pregnancy introduces a few more problems than tetany without pregnancy. The paresthesias and "leg cramps" of so many pregnant women may resemble the onset of tetany. The blood chemistry studies are invaluable and Ellsworth⁶⁵ establishes values of serum calcium below 8.5 mg. and serum phos-

phorus above 4.5 mg. as definite criteria of hypoparathyroid insufficiency. In addition to these findings, Albright⁶⁶ includes x-ray pictures revealing normal bone structure and the absence of renal insufficiency to establish a diagnosis of chronic idiopathic hypoparathyroidism.

The low serum calcium and elevated serum phosphates produce hyperirritability of the peripheral neuromuscular system, and various forms of muscle spasms, such as carpopedal and laryngospasm, may develop. Breathing may become difficult and actual convulsive seizures of the tonic type simulating epilepsy may occur. In the differential diagnosis, if convulsions are the presenting complaint, the more common obstetric convulsions of eclampsia and also hypoglycemia, epilepsy, meningitis, hysteria, and brain tumors must be kept in mind.

The classical Erb, Chvostek, and Trousseau signs are of some value. Kehrer¹ showed the Chvostek sign to be positive in 75 per cent of all pregnant women. Pollak³⁰ corroborated these findings. The cathode closing contraction is present in 80 per cent of pregnant women, illustrating an increase of neuromuscular excitability.

Eaton and Haines⁷¹ made interesting observations with x-rays of the skulls of patients with chronic parathyroid insufficiency. They were able to demonstrate symmetrical cerebral calcification and also calcification of the basal ganglia in some of their cases.

Hartley⁷² called attention to a condition in the pregnant woman which he termed "the tetanoid syndrome." Konikow⁵² described a similar condition in which calcium lactate and para-thor-mone gave complete relief.

Many of the cases of "hyperventilation tetany," occurring at the time of delivery, described by Klasten,⁴⁹ appeared to be similar to the tetanoid syndrome and responded well to calcium therapy alone.

There are a few alterations in the physiology of the pregnant female which must be considered.

Bodansky and Duff⁷³ examined a large series of normal pregnant women in which serum calcium values of 8 to 8.5 mg. per 100 c.c. were obtained in 24 per cent. Plass and Bogert⁷⁴ elicited serum calcium values below 9 mg. per 100 c.c. in 50 per cent of pregnant females during the last five months of the gestation. Richardson⁴⁷ had similar values, although in one case under his observation a serum calcium value of 5.6 mg. per 100 c.c. was obtained without subsequent symptomatology.

Bokelmann and Bock⁷⁵ demonstrated an increase of serum calcium during labor over the slight decrease observed during the pregnancy. During delivery a decrease in serum calcium occurs followed by a return to the normal value in the puerperium. These investigators showed that the total calcium and diffusible calcium is higher in the cord blood of the newborn than that in the maternal blood.

Bogert and Plass,⁷⁴ Bodansky and Duff⁷³ maintained that the significant correlation between protein and calcium concentrations in non-pregnant and puerperal women is completely lost in late pregnancy. They feel that the role of the placenta in producing an intrinsic calcium depressing agent may be the answer for the lower blood calcium levels in the latter half of pregnancy.

Hoffmann and Rhoden⁷⁶ first described a substance in the blood of pregnant women which when injected into dogs caused an increase in their serum calcium. In this respect, the substance resembled parathyroid hormone. In addition they calculated that one liter of pregnant women's blood contained the equivalent of 18 Collip units of para-thor-mone. Bomskov and Bremm⁷⁷ had also postulated a substance in the placenta resembling parathyroid hormone. Hamilton, Dosef, Highman and Schwartz⁷⁸ made similar observations, and found increased amounts of the hormone between the fifteenth and thirty-fifth weeks of normal pregnancies.

A great deal of experimental work has been done on the relationship of the parathyroid glands and pregnancy. We will include only a few pertinent references.

Dragstedt, Sudan and Phillips⁷⁹ completely removed the thyroid and parathyroid glands of dogs. During pregnancy, tetany developed in all degrees of severity. Such an attack of tetany not immediately fatal to the mother usually resulted in the death of the fetuses followed by abortion. Dogs with tetany could be easily controlled by administration of Ringer's solution and 15 to 30 Gm. of calcium lactate daily, fed through a stomach tube. Larson and Fisher⁸⁰ demonstrated similar findings.

Bodansky and Duff,⁸¹ working with rats having parathyroid deficiency, demonstrated a markedly diminished fertility and reduction in the number of newborn rats in the litter. Tetany at term, prolonged labor, and high rates of maternal and fetal mortality were also observed. If these parathyroid deficient rats were fed a diet abnormally high in calcium and relatively low in phosphorus, the serum calcium was increased and the serum phosphorus was decreased. The abnormal manifestations of late pregnancy were likewise abolished, and the differences in fertility, the average number of newborn per litter, and the average birth weight were greatly minimized.

To the obstetrician these experimental facts must be kept in mind, because they bear a most important relationship to the human pregnant female. Of course variations in the human pregnant female with parathyroid insufficiency and the lower species of life occur. The possibility of accessory parathyroid tissue in various species of life has been advanced as an explanation for these variations.

TREATMENT

The problem of therapy in hypoparathyroidism is to elevate the blood calcium and decrease the serum phosphate. In a case of impending convulsions calcium preparations may be given intravenously. For this purpose 10 to 20 c.c. of a 10 per cent calcium gluconate solution is very effective. Parathyroid extract may also be used during the acute stage but not over a long interval of time, because of the increasing tolerance of the patient to para-thor-mone and also because of the cost of the drug.

After the acute stage of the disease has subsided calcium lactate may be administered orally. An average daily dose of 25 to 30 Gm. is prepared by adding this amount to the minimum amount of warm water necessary to dissolve the calcium lactate. The solution is then divided into 4 or 5 equal portions to be taken at regular intervals while the patient is awake. It is also beneficial to place the patient on a low phosphorus diet by limiting the intake of meats, glandular tissue, cheese, milk, and egg yolk. More fruits, vegetables, fats, and carbohydrates are substituted in the diet.

Thyroid extract has been used. Aub⁸² and his colleagues feel that it increases phosphorus excretion.

Such a program deals only with the calcium and phosphorus intake. To increase the intestinal absorption of calcium, vitamin D in the form of viosterol was used until the newest therapeutic agent, dihydrotachysterol was discovered.

Dihydrotachysterol (A. T. 10) was introduced by Holtz⁸⁴ in 1933. It is derived from the irradiation of ergosterol in which tachysterol is converted to dihydrotachysterol preparation. It is prepared as a 0.5 per cent solution in oil, and as advocated by Albright⁸³ and other investigators, an initial dose of 3 to 10 c.c. orally may be used. Even 3 c.c. daily may be continued for a week, finally reducing to a maintenance dose of 1 c.c. three times per week. The dosage varies with the individual patient, and during administration it is most important to determine the serum calcium at frequent intervals. A less accurate guide is the Sulkowitch test⁸⁴ in which equal amounts of Sulkowitch reagent and urine are mixed in a test tube. A milky precipitate is a danger sign indicating a high calcium excretion and an elevated serum calcium. A clear solution is interpreted as meaning a value of 5 to 7.5 mg. calcium per 100 c.c. of blood. At this point dihydrotachysterol should be administered until the repeated urinalyses show a fine white cloud which is the desired range of blood calcium, approximately 9.5 mg. per 100 c.c. of blood. Excessive doses of dihydrotachysterol produce polyuria, thirst, nausea, abdominal cramps, vertigo, and tinnitus. Also, the possibility of metastatic calcification in the kidneys must be entertained.

In summarizing the effectiveness of the three preparations, parathormone, vitamin D, and dihydrotachysterol, it is important to remember that each one has its particular use and in the management of any one case all three preparations may be used to the distinct advantage of the patient.

Vitamin D and dihydrotachysterol increase calcium absorption from the intestine and also increase phosphorus excretion, but dihydrotachysterol has more effect on phosphorus excretion than vitamin D. Parathormone, on the other hand, is more effective in elevating the blood calcium than dihydrotachysterol, but dihydrotachysterol has a more prolonged effect.

Holtz^{36, 61, 85} and his co-workers called attention to the increased amounts of A. T. 10 necessary during menstruation and pregnancy. In a recent paper, Holtz⁸⁵ advocated large single doses (8 to 15 c.c.) if marked hypocalcemia was present. In some cases 20 c.c. might be given at a single dose. Holtz⁸⁵ had shown that experimentally in the dog the last quarter of the pregnancy was most dangerous. In the human pregnant female, the fourth and fifth months were the months in which symptoms of tetany would develop. During the second half of pregnancy, the daily dosage of dihydrotachysterol may be tripled. Holtz³⁶ called attention to several factors in the pregnant human female, occurring during the fourth month which might explain the occurrence of tetany in those particular months. In the fourth month of pregnancy the theelin production increases and the placenta begins its control of the pregnancy. The placenta may produce a calcium depressing substance. Also at this time the growth of the fetus is rapid and deposition of calcium in the bones of the fetus takes place. All of these factors place demands on the maternal calcium supply and tend to lower the available calcium. With the onset of labor, all A. T. 10 should be stopped. In six years' experience with dihydrotachysterol (A. T. 10), Holtz⁸⁵ has encountered no difficulties. He felt that the dangers of hypercalcemia were minimal and lately suggested using theelin to lower the serum calcium if hypercalcemia developed. Perhaps stilbestrol could also be used for this purpose.

The advantages of A. T. 10 over para-thor-mone are its cheapness and it can be given orally. In addition no tolerance develops as is the case with para-thor-mone.

CASE REPORTS

CASE 1.—Mrs. P. G., a 23-year-old white, married female, was admitted to the Buffalo General Hospital on Nov. 13, 1921, complaining of nervousness, tremor, loss of weight, exophthalmos, increased heart rate, and increased perspiration, particularly of the hands. These symptoms had been present for six months and were increasing in severity.

Physical examination revealed a slightly undernourished white female with a palpable thyroid, lid lag, widening of the palpebral angles, rapid heart rate, exophthalmos, and "clammy" hands and feet. A fine tremor was also present. The basal metabolic rate was plus 68 per cent. A clinical diagnosis of Graves' disease was made.

Surgery was suggested on several occasions but the condition of the patient did not warrant the operation. The patient was sent to a convalescent home for rest.

The patient was re-admitted to the hospital, and on March 14, 1922, under nitrous oxide-oxygen anesthesia, the left side of the thyroid was resected and the right superior thyroid vessels were ligated. Pathologic examination revealed the characteristic findings of Graves' disease. Two weeks after surgery a basal metabolic rate was plus 9.5 per cent. The patient was discharged in good condition on April 1, 1922.

She remained free of symptoms for ten years following thyroideectomy until 1932 when she observed an enlargement of her neck in the location of the thyroid gland, weight loss, dyspnea, and difficulty in swallowing.

It was decided to admit her to the hospital for the third time, and on Oct. 2, 1934, under avertin-nitrous oxide-oxygen anesthesia, a large right lobe of the thyroid gland (measuring 8 by 5 by 3 cm. in thickness) was removed and a smaller portion of the left lobe of the thyroid was also removed. Pathologic examination revealed findings of Graves' disease.

Nine days following surgery the patient developed numbness and tingling in her extremities associated with tremors and jerking movements. Chvostek's and Trousseau's signs elicited at this time were positive. The serum calcium was 5 mg., and the serum phosphorus was 9.1 mg. per 100 c.c. of blood. A diagnosis of parathyroid insufficiency was made. Treatment with intravenous calcium chloride relieved the patient's symptoms. Improvement was rapid, and the patient was discharged from the hospital on Nov. 28, 1934. She continued to take calcium in the form of calcium chloride (diluted with water) and viosterol as the various symptoms presented themselves. If paresthesias or muscle spasm developed, it could be relieved by drinking calcium chloride solution and viosterol until the symptoms disappeared. In this fashion her daily existence was tolerable until Aug. 19, 1939. At this time "blinking" of the eyelids and carpopedal spasm had developed which could not be controlled by the usual oral ingestion of calcium chloride. Nausea and vomiting, with amenorrhea of two and one-half months' duration, suggested possible pregnancy which was confirmed by vaginal examination and a Friedman test. The obstetric history revealed that the patient was the mother of seven children, all of whom had been born before 1934, the year in which she developed postoperative tetany. Three "miscarriages" were also noted in the past history.

Physical examination at this time presented positive Chvostek's and Trousseau's signs. Skull x-ray films did not show evidences of cerebral calcification (Fig. 1). The question of therapeutic abortion was raised at this time, but because of the encouraging response with dihydrotachysterol and oral calcium lactate, no reason for such a procedure could be advanced. In Fig. 2 the medication and blood chemistry findings are illustrated.

The prenatal course after regulation with dihydrotachysterol was uneventful, although on one occasion two weeks before term a slight elevation of blood pressure was observed. At this time suspicion of death of the fetus was postulated (absence of fetal movements and failure to elicit fetal heart sounds).

On Feb. 24, 1940, a normal female child weighing 2,740 Gm. and 48.5 cm. in length was delivered without any difficulty. The first stage was twelve hours, the second stage lasted fifteen minutes, and the placenta delivered four minutes after the baby. No abnormal bleeding occurred. The patient nursed her baby throughout the hospital stay. During the two weeks following delivery, a maintenance dose of $\frac{1}{2}$ e.e. of dihydrotachysterol was administered. Thirty grams of calcium lactate were given as a daily dosage.

In the late puerperium and the months following delivery, the expense of dihydrotachysterol prevented the patient's daily use of the drug, and as Fig. 2 illustrates, the return of symptoms occurred during the periods when dihydrotachysterol was not administered. The patient and her baby have been seen at irregular intervals during the past fifteen months. Manipulation of the calcium lactate and A. T. 10 by the patient has been fairly successful in the control of symptoms.

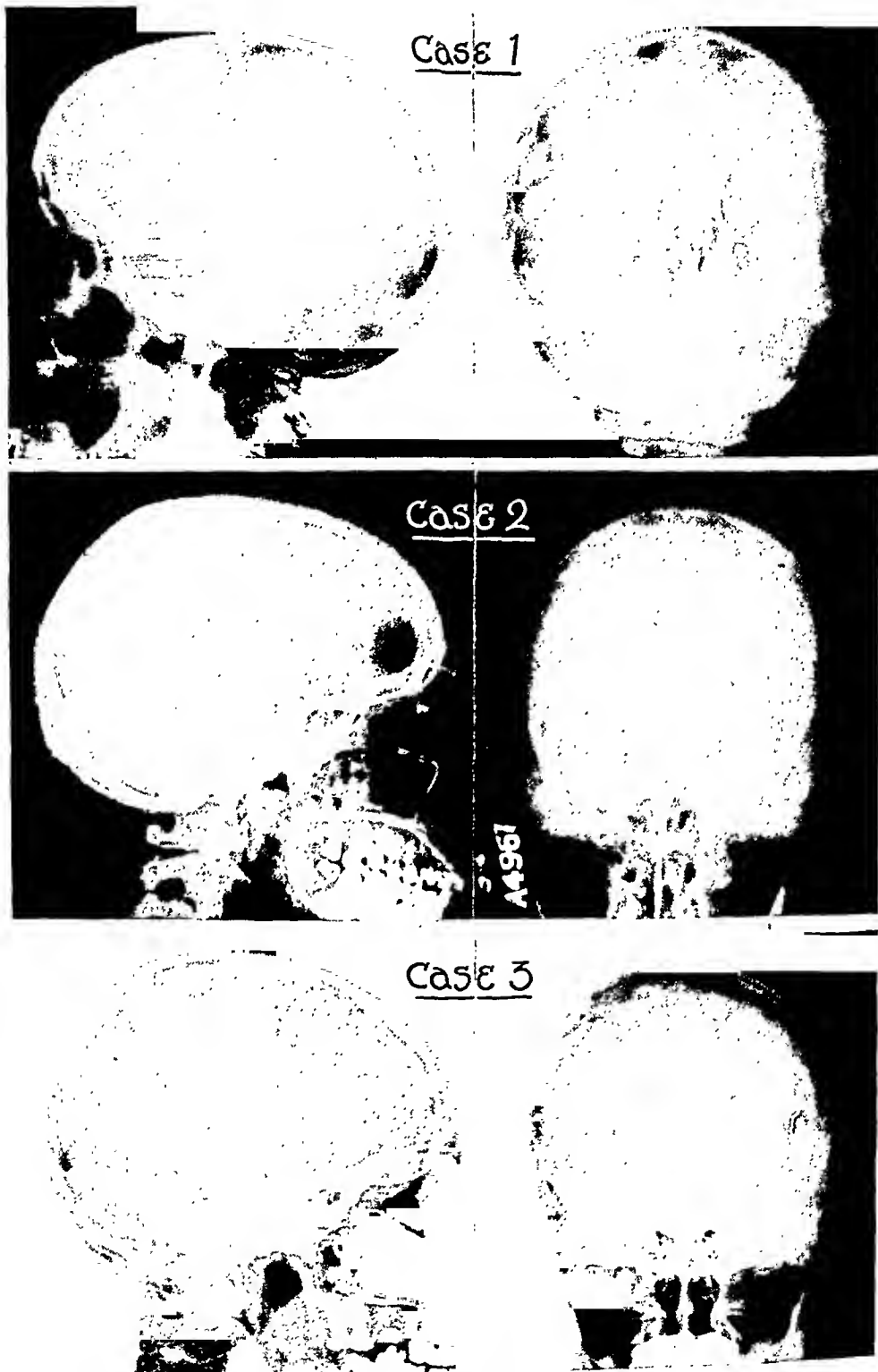


Fig. 1.—X-ray views of the skulls of patients in Cases 1, 2, and 3, illustrating absence of cerebral calcification in Cases 1 and 2 with some abnormal calcification in the frontal region of Case 3.

Blood chemistry studies on April 1, 1941, revealed a serum calcium of 8.4 mg. and a serum phosphorus of 5.6 mg. per 100 c.c. of blood serum.

CASE 2.—Mrs. C. L., a 28-year-old white, married female, was admitted to the Buffalo General Hospital on March 26, 1939, with a "swelling" of the neck which had become worse since the birth of her last baby in 1938. Her past history was essentially negative. She had 8 living children and 3 "miscarriages." Physical examination was entirely normal except for an enlarged thyroid gland with a nodule in the left lobe.

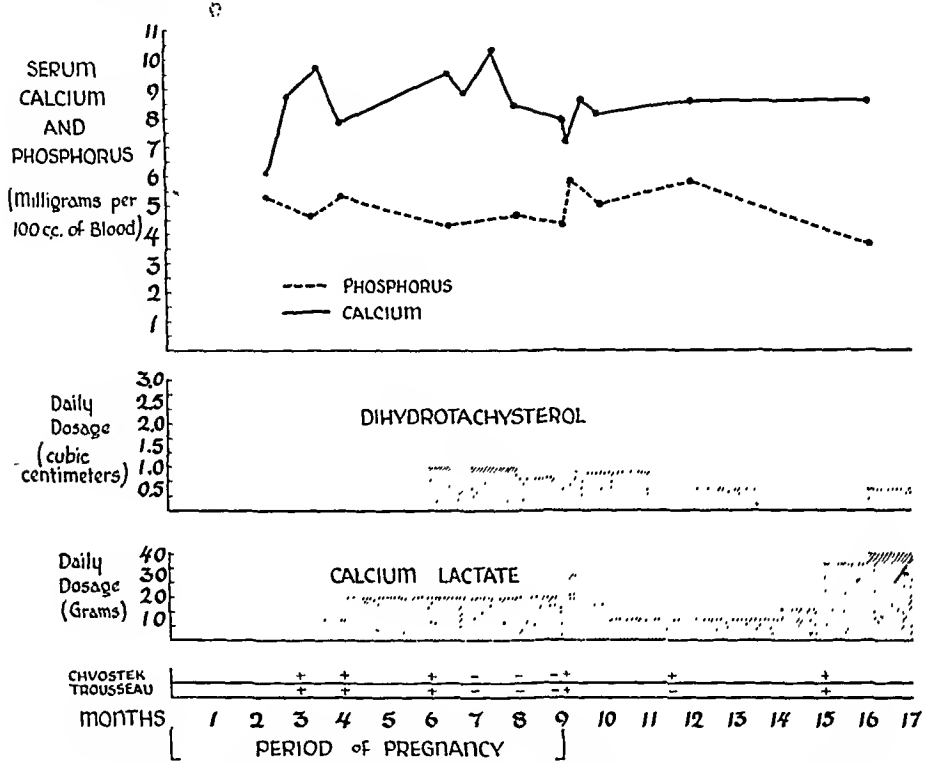


Fig. 2.—Graph showing the serum calcium and phosphorus values, the daily dosage of dihydrotachysterol, and oral calcium administered, and various symptoms observed in Case 1 (Mrs. P. G.).

On March 27, 1939, under nitrous oxide-oxygen-avertin anesthesia, the major portion of the left lobe of the thyroid was resected and part of the right lobe was also resected. Pathologic diagnosis of the specimen was a simple diffuse colloid goiter.

Two days postoperatively the patient developed tingling sensations in her hands and slight carpedal spasm was observed. The serum calcium at that time was 7.9 mg. Calcium gluconate was given intravenously and a daily dosage of 40 Gm. of calcium lactate combined with vitamin D was administered orally.

The patient was discharged eight days after surgery. Although she had a positive Chvostek's sign and a slightly positive Trousseau's sign her clinical condition was excellent. She remained on large doses of oral calcium lactate and viosterol at home until her next visit to the outpatient department on Nov. 21, 1939, approximately eight months postoperatively.

At this time her complaint was amenorrhea of two months' duration. Examination revealed a two months' pregnancy. A slightly positive Trousseau and a positive Chvostek sign were observed. The serum calcium was 11 mg. and the serum phosphorus was 5.7 mg. per 100 c.c. of blood. With such an excellent blood chemistry, it was deemed advisable to allow the pregnancy to continue and the medication to consist merely of oral calcium lactate and vitamin D. However, as the pregnancy approached term, the patient's complaints of paresthesias and muscle spasms increased, and as Fig. 3 demonstrates, the serum calcium level decreased to a value of 6.4 mg. Coincident with these findings, an elevation of blood pressure and the appearance of albumin in the urine, warranted hospitalization. X-rays of the skull did not

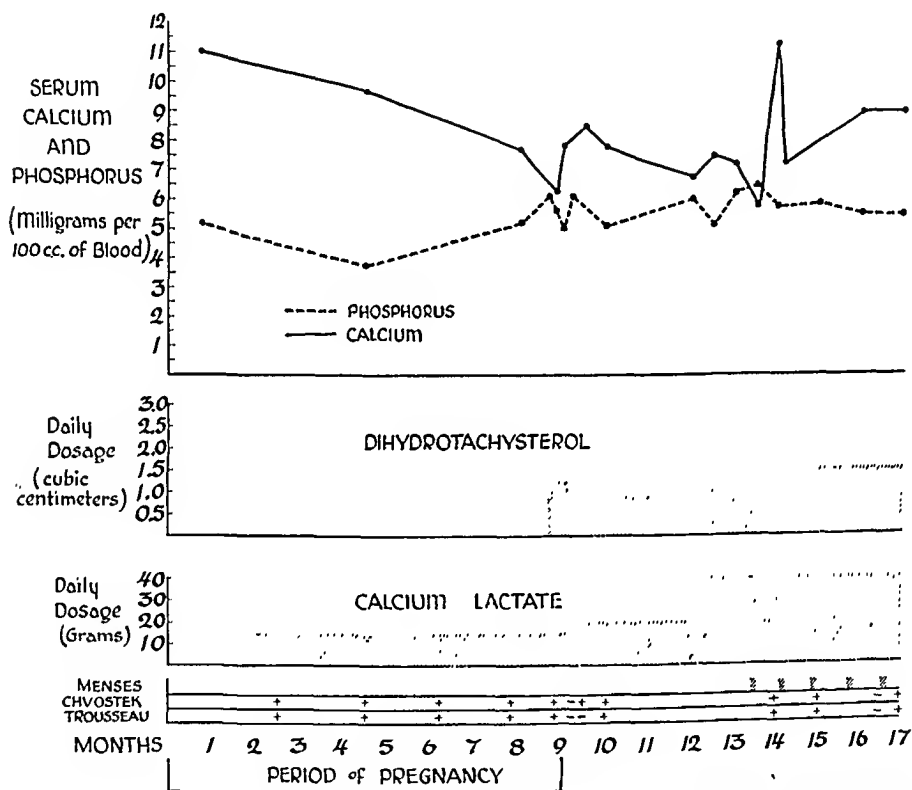


Fig. 3.—Graph showing the serum calcium and phosphorus values, the daily dosage of dihydrotachysterol and oral calcium administered, and various symptoms observed in Case 2 (Mrs. C. L.).

show evidences of cerebral calcification (Fig. 1). Dihydrotachysterol beginning with a daily dosage of 0.75 c.c. increasing to 1.3 c.c. was administered for two weeks. Calcium lactate intake averaged 15 Gm. daily. In addition, vitamin D and a low phosphorus diet (particularly no milk) were prescribed.

On June 15, 1940, after a surprisingly short first stage labor (less than one hour), the patient was delivered of a normal female infant weighing 3,400 Gm. and measuring 52.5 cm. in length. No difficulty was encountered in delivery of the placenta which was delivered six minutes after the birth of the baby. It is interesting to note the length of labor of less than one hour, because the entire personnel of the

obstetrics division did not appreciate the presence of labor pains until the head was presenting on the perineum. The patient insisted that she did not have "pains" or uterine contractions until twenty to thirty minutes before delivery. She nursed her baby during the stay in the hospital without deleterious effects.

On discharge from the hospital the patient continued to take 0.75 c.c. of dihydrotachysterol and 20 Gm. of calcium lactate for about two months. As illustrated in Fig. 2, she did not take the medication for two months. This was followed by return of symptoms. Resumption of the previous regimen of therapy with dihydrotachysterol alleviated her symptoms, and the cooperation of the patient increased as she experienced these periods of remission due to failure to take a daily dose of dihydrotachysterol. At the present time, she is in excellent condition. Her baby is also in excellent health.

CASE 3.—Mrs. M. B., a 33-year-old white female, a private patient of Dr. B. D. Bowen, developed parathyroid insufficiency on the fourth post-operative day following thyroidectomy in 1929. The operation was performed for cosmetic correction of a huge colloid goiter. Carpopedal and laryngospasm developed on the fourth postoperative day but relief was obtained with intravenous calcium and para-thor-mone subcutaneously. The patient was married in 1930 and during her first pregnancy developed slight twitchings of muscles and crampy pains in the legs which were alleviated by oral calcium lactate and viosterol.

After a ten-hour labor on Feb. 13, 1932, the patient delivered a 4,386 Gm. male infant. At the time of delivery carpopedal spasm and muscular twitchings were observed. The patient weighed 164 pounds before pregnancy and gained 35 pounds during the gestation. A basal metabolic rating at this time was plus 12. Due to insufficient milk supply, the baby was taken off the breasts. At the present time no abnormalities have been noticed in the growth and development of this child.

In the sixth post-partum week, the patient developed "rigid arms" and other signs of tetany which were relieved by calcium orally. This attack was followed by another episode with the onset of the first menstrual period following delivery. During the next two years the patient gained approximately 50 pounds in weight. Coincidental with the gain in weight the symptoms of tetany increased in severity. A physician prescribed additional calcium therapy and a weight reduction diet. Thyroid extract and some form of pituitary extract were added, and the patient was able to lose 50 pounds of weight. Her symptoms of tetany disappeared except at the menstrual periods, during which calcium lactate in 4 Gm. doses was taken until the symptoms disappeared.

In 1935 Mrs. M. B. had a spontaneous abortion of eight weeks' gestation and in 1937 became pregnant for the third time. During the pregnancy the symptoms referable to tetany disappeared.

On Nov. 12, 1937, after a peculiar first stage of labor (the patient apparently had no "pains"), the patient delivered a 3,772 Gm. male infant. No abnormal bleeding was noticed. The serum calcium was 7.9 mg. per 100 c.c. of serum and the serum phosphorus was 6.5 mg. per 100 c.c. of serum. With the onset of the patient's first menstrual period after delivery, which occurred in February, 1938, the symptoms of tetany recurred. It was shortly after this time that the patient presented herself to Dr. B. D. Bowen for treatment.

On April 6, 1938, physical examination revealed an obese, 33-year-old female, 65.5 inches tall and weighing 203.5 pounds. Her blood pressure was 105 systolic and 70 diastolic. Chvostek's and Trousseau's signs were positive. Serum calcium was 5.9 mg. per 100 c.c. of serum and phosphorus was 3.6 mg. X-ray films of the patient's skull are shown in Fig. 1. The patient was placed on varying doses of calcium gluconate and dihydrotachysterol. During the menstrual periods, 3 c.c. of dihydrotachysterol would be given each day for three to four days.

After observation for one month patient became pregnant. The calcium, phosphorus, and medications are illustrated in Fig. 4.

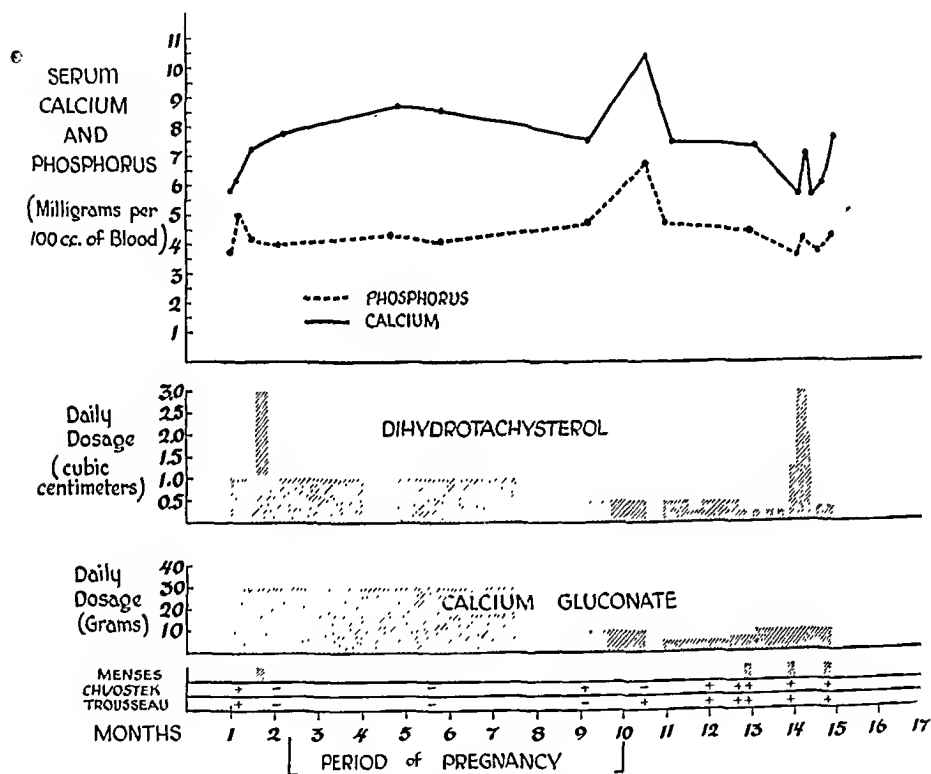


Fig. 4.—Graph showing the serum calcium and phosphorus values, the daily dosage of dihydrotachysterol and oral calcium administered, and various symptoms observed in Case 3 (Mrs. M. B.)

On Jan. 17, 1939, the patient delivered her third normal infant, after a twenty-hour labor. The infant weighed 3,632 Gm. It is interesting to note that this patient improved during the pregnancy even though she did not adhere to the therapy prescribed and would go intervals of one to two weeks without medication. But since delivery control of the symptoms has been difficult, particularly during menstruation. Anticipation has on a few occasions (when the patient's cooperation has been obtained) prompted increasing the doses of dihydrotachysterol three or four days before the menses and prevented the occurrence of tetany.

Observations of the patient have been spasmodic during the past sixteen months, but she has continued to have tetany during the period of menstruation. Because of the obesity and the possible combination of hypothyroidism and hypoparathyroidism, a recent attempt to place the patient on a diet has been made. Thyroid has also been prescribed.

CONCLUSIONS

A review of 240 cases of tetany in pregnancy, occurring in the previous literature has been presented. Classification of the cases into four types was attempted. Twenty-six cases were of the postoperative hypoparathyroid type of tetany with pregnancy; 145 were of the idiopathic or spontaneous type, including in this group those cases which occurred during the pregnancy, during delivery, or in the post-partum period. The third type consisted of a dietary type, due to low calcium intakes and vitamin D deficiencies, of which 9 cases were reviewed. The last type included 60 cases of tetany associated with thyroid deficiency disease.

The early literature stresses the relationship of the female sex organs and pregnancy in the development of tetany. Other more specific factors, such as menstruation, lactation, blood loss at time of delivery, hyperventilation, and low calcium intakes, have been considered.

In previous years tetany in pregnancy was considered an indication for therapeutic abortion, because of the high fetal mortality rate, also the tendency of newborn infants to develop tetany, and a definite maternal mortality rate. Treatment consisted of potassium bromide, chloral hydrate, venesection and premature induction of labor. Milk diets, ox parathyroids by mouth, and in recent decades parathyroid gland transplantations have been used without successful results.

During the past decade evidence has been accumulating which offers a much better prognosis for both the pregnant mother and her baby. A combination of oral and intravenous calcium preparations, parathormone, and dihydrotachysterol (A. T. 10) carefully regulated by the patient and her physician yielded successful results in 12 of 13 cases in the literature (includes 3 cases of postoperative type presented by the authors). Pre-eclamptic toxemia was present in the one unsuccessful case and premature induction of labor was necessary. In our 3 cases pre-eclampsia occurred twice. Therefore, we feel that concurrent toxemias must be watched for in cases of tetany in pregnancy. No abnormal alterations of the labors or delivery were observed. Careful observations of mothers and babies revealed no unusual abnormalities. It is our contention that therapeutic abortion is rarely indicated in the light of present-day therapy advocated for cases of tetany in pregnancy.

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RENAL FUNCTION STUDIES IN NORMAL PREGNANCY AND IN TOXEMIA BASED ON CLEARANCES OF INULIN, PHENOL RED, AND DIODRAST*

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THE relationship of the kidney to the pathologic and clinical picture of eclampsia and pre-eclampsia remains, after a century of discussion, an unsettled point. On account of the proteinuria, the edema and the convulsions, eclampsia was considered at first to be closely related to Bright's disease.^{18, 30} Later, and for a few years, the striking hepatic lesions seized the center of medical attention and the liver was assigned an important position in the causation of at least certain cases of toxemia.^{27, 38, 39} More recently the vascular changes, especially those in the small arterioles, have come to be considered the basis of the disease, a view advanced by Volhard⁵⁴ and recently strongly emphasized by some

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American physicians.^{15, 24-26} Nevertheless, a belief in the importance of a renal factor has persisted as evidenced by the number of cases still being classified as chronic nephritis or renovascular disease in pregnancy.^{11, 14, 49, 50}

Because of recent advances in renal physiology, further consideration must now quite evidently be given to the kidney in toxemia. The experiments of Goldblatt and his followers on the effects of interference with the renal blood supply on the arterial pressure and the discovery of various pressor substances of renal origin have indeed turned the investigation of all conditions associated with hypertension toward the kidney. In the group of diseases with hypertension, specific toxemia of pregnancy is of course one of the most striking.

Histologic study of the kidneys from patients dying of eclampsia or pre-eclampsia has led to the description of a variety of lesions.

Degenerative changes in the tubules were long regarded as important, and recent investigators have continued to report their presence.⁵⁷ Glomerular damage, which appears to have been first described in 1918 by Lohlein,³¹ has in recent years received the most attention. According to Fahr's¹⁶ classical description published in 1924, the essential kidney lesion consists in a swelling of the capillary walls, with the result that the lumina are narrowed and the glomeruli appear relatively anemic. Fahr regarded the lesion as degenerative, a "glomerulonephrosis." Other observers^{1, 2, 28} have in general confirmed these findings, but some tended to regard the lesion as inflammatory, a form of glomerulonephritis. An additional observation of Fahr was the thickening and swelling of the walls and the proliferation of cells occasionally observed in the afferent arterioles to the glomerulus, a feature not stressed by most other writers.

These glomerular lesions have now been recognized for at least twenty years. Yet little significance has been accorded them by the clinician, perhaps because of his own failure to demonstrate disturbance in renal function by any of the commonly accepted tests. There is in toxemia little or no alteration in the blood urea or the maximum specific gravity of the urine. Phenolsulphonephthalein excretion is unaffected and changes in the urea clearance are not consistently present.^{3, 5} It has not been possible then to find a reflection of the observed renal lesions in disturbed renal function.

In this report there will be described the results of kidney function tests as determined by the renal clearances of a series of normally pregnant and pre-eclamptic women. These tests are based on the principle employed in urea clearance but utilize such substances as diodrast and inulin, which are capable of distinguishing tubular from glomerular function, and give in addition indications of the condition of the blood vessels supplying the active portions of the kidney.

RENAL ANATOMY AND PHYSIOLOGY

It may be necessary to recall a few facts about renal anatomy and physiology. The kidney is made up of about a million more or less independent units or nephrons. Each such unit begins in the cortex as a funnel-shaped structure (Bowman's capsule) which surrounds a tuft of capillaries to form the glomerulus. Beyond Bowman's capsule, the nephron widens out into the proximal convoluted tubule which is lined with large pyramidal cells. The tubule then becomes thinner and straighter and makes a long excursion toward the kidney pelvis. From there after making a loop it returns to the cortex, where it once again widens and becomes tortuous as the distal convoluted tubule. Finally it turns a second time toward the pelvis into which it empties through the collecting ducts.

The organization of the arterial supply to these segments of the nephron has become a subject of prime importance because of the relationship of the renal blood supply to hypertension. After repeated divisions of the renal artery, a branch enters the glomerulus as the *afferent arteriole*. This breaks up within Bowman's capsule into a number of capillary loops, the glomerular capillaries, which later join to emerge from the glomerulus as the *efferent arteriole*. This arteriole divides into a second capillary system which supplies the tubules of both the proximal and distal segments. Thus the blood which reaches and supplies the kidney tubules has had first to traverse in succession the afferent arterioles, the glomerular capillaries and the efferent arterioles. Functional or organic disorder in these segments of the kidney's vascular system may then have an effect on tubular as well as on glomerular function.

Studies of renal physiology have established different functions for glomerulus and tubules. The glomeruli act as simple filters through which pass all the constituents of the plasma with the exception of the proteins, to which the glomeruli are normally impermeable. The glomerular fluid is protein-free plasma with the solutes in concentrations equal to those in the plasma. This glomerular fluid in its course down the nephron undergoes changes as a result of reabsorption and excretion through the cells of the tubules. Water and other substances, such as glucose, sodium chloride and urea, are reabsorbed in varying amounts. Other types of material, such as creatinine and the dyes used for kidney function tests, are excreted by the tubules.

SIGNIFICANCE OF RENAL CLEARANCES

The studies of kidney function in pregnancy here presented, are based on the conception of renal "clearance." It was originally used by Van Slyke³³ and his associates in 1928 in connection with the excretion of urea. Urea clearance has been defined as the volume of

blood which one minute's excretion of urine suffices to clear of urea. The figure for urea clearance could therefore be obtained from the formula $\frac{UV}{B}$ where U = concentration of urea in the urine, V = the cubic centimeters of urine formed in a minute and B = the blood concentration of urea. If plasma clearances are used, the formula becomes $\frac{UV}{P}$ where P is the urea concentration of the plasma.

The urea clearance test is a much more sensitive indicator of renal insufficiency than the simple determination of blood urea. Yet it has some limitations, for although urea is completely filtered at the glomerulus and begins its passage through the nephron in concentration equal to that of the plasma, about 40 per cent is reabsorbed by the tubules. Thus, although its clearance in the normal kidney parallels the glomerular filtration rate, it does not directly measure that function.

In the last few years the concept of renal clearance has been extended to other substances which do measure glomerular or tubular function. Only the briefest discussion can be given here to a subject upon which there is already a very extensive literature.

1. *Inulin Clearance*.—Inulin, a polysaccharide of high molecular weight, is filtered at the glomerulus and is neither absorbed nor excreted by the tubules.^{37, 41, 42} The renal clearance of inulin is therefore a measure of the rate of glomerular filtration. In normal women the filtration rate amounts to 119 c.c. per minute.²¹

The glomerular filtration rate depends upon the character of the capillary wall and upon the pressure available to force the fluid through. Changes in the character of the capillary walls may alter their permeability and thus the filtration rate. Changes in the filtration pressure may result from alterations on the one hand in the intracapillary, on the other in the intracapsular pressure. Increase in the intracapsular pressure opposes filtration and may result from an increase in interstitial tension of the kidney as, for example, from edema or from urinary tract obstruction. A rise in the intracapillary pressure favors filtration and may be produced by an increase in the systemic arterial pressure, by constriction of the efferent arteriole or by dilatation of the afferent arteriole. A fall in filtration pressure, on the other hand, will result from a drop in arterial blood pressure, constriction of the afferent arteriole, or dilatation of the efferent arteriole. Changes in the plasma protein concentrations, so far as they affect oncotic pressure, influence filtration rates to a small extent. These aspects of renal physiology have recently been analyzed in detail in a paper by Smith and his associates.⁴⁷

2. *Phenol Red and Diodrast Clearance*.—Tubular excretion may be studied with the aid of a variety of substances, two of which have been used in the cases of this study, namely, phenol red and diodrast. Al-

though phenol red is rapidly excreted by the tubules, diodrast is handled still more efficiently. Diodrast indeed has the highest clearance of any known substance and is believed to be almost entirely removed from the plasma as the blood passes from the renal artery to the renal vein. For this reason its clearance measures the minimum volume of plasma which must have flowed to the excretory tissue of the kidney during the given time. The plasma diodrast clearance, if the hematocrit is known, can be converted into a figure for *the effective renal blood flow*. This has been found for normal males to amount to an average of 1,189 c.e. per minute, for normal women to 996 c.e.²¹

Renal blood flow, other factors being equal, will vary directly with the arterial blood pressure. Constriction or dilatation of the renal vascular system, in particular the afferent and efferent arterioles of the glomerulus, will also vary the renal blood flow.

3. *Tubular Excretory Mass*.—When the plasma level of diodrast is raised to the point where the tubule cells become saturated, the excretion of this substance reaches a maximum rate. This is constant under standard conditions in any individual and serves as a measure of the total functioning tubular tissue.⁴⁸ It is referred to as *the tubular excretory mass*, or *diodrast Tm*, and is reported as milligrams of iodine excreted per minute. Absolute clearance values vary in different normal individuals over a fairly wide range, but when clearances are related to diodrast Tm, these differences largely disappear.²¹

4. *Filtration Fraction*.—It is often useful to compare glomerular and tubular function by studying the ratios between the clearances of substances handled more or less exclusively by the one or the other. The inulin/diodrast clearance ratio is known as the *filtration fraction* and has a special significance. Since the inulin clearance is a measure of glomerular filtration rate and the diodrast clearance of the minimal plasma flow to active excretory tissue, the filtration fraction represents the proportion of the effective circulating plasma which is filtered at the glomerulus.

From the filtration fraction inferences are made regarding the status of the efferent arteriole, the tone of which is believed primarily to determine renal blood flow.⁴⁵ Constriction of the efferent arteriole will reduce blood flow, but as a result of raised intracapillary pressure in the glomerulus, the rate of glomerular filtration will be maintained and an increased filtration fraction will result. Spasm of the afferent arteriole, if it occurs, should reduce the pressure in the glomerular capillaries and produce a reduced filtration fraction.

PREVIOUS INVESTIGATIONS

The application of these methods to the study of clinical problems has already been extensive. In essential hypertension there has been

demonstrated by Goldring and his associates^{20, 22} a diminished renal blood flow, a maintained or lowered rate of glomerular filtration, and a consequently increased filtration fraction. This they interpret as evidence of hypertonus of the efferent arteriole of the glomerulus.

In both normal and pre-eclamptic patients, Chesley and his associates^{6, 7} have observed that the effective renal blood flow as measured by the diodrast clearance is normal. Corcoran and Page⁹ have reported in toxemia of pregnancy a diminution in filtration rate as measured by inulin clearance associated with a normal effective renal blood flow, as measured by phenol red or diodrast clearance.

TECHNICAL METHODS OF PROCEDURE

Cases for this study were patients either under treatment for specific toxemia in the obstetric ward at Bellevue Hospital or were normal pregnant women admitted for study from the prenatal clinic. In all instances efforts were made to repeat the tests after delivery either just before the patient's discharge from the hospital or by readmitting her for the purpose at some later date.

The technique used in making these observations has been described in detail elsewhere.^{48, 56} A few general principles may be noted. The tests are undertaken in the morning with omission of the patient's breakfast, although large quantities of water are prescribed the night before and shortly before the work is begun, to increase the urine flow. The necessary blood concentrations of the substances whose clearances are to be studied are maintained by continuous intravenous infusion at a controlled rate. The actual plasma concentrations are determined from blood samples obtained at regular intervals. The urine is collected at the end of each period by catheter, the bladder being washed out with measured quantities of normal saline to insure complete emptying. Special difficulties in the emptying of the bladder may be encountered in pregnant patients if the fetal head is low in the pelvis.

RESULTS

Three types of patients have been studied. First, there have been women who have remained normal throughout their pregnancy and in their puerperium. Next is a group of patients with specific toxemia who made a rapid and complete recovery after termination of their pregnancy. The third is a group of patients with toxemia whose hypertension persisted after delivery. The division of the toxemia patients on the basis of post-partum blood pressure was made after observation in the follow-up clinic.

Results have been published elsewhere in detail.^{55, 56} Here only average ante-partum and post-partum figures will be presented with a single chart, illustrating the characteristic findings in two patients, both with toxemia but with contrasted post-partum blood pressure behavior.

Normal Pregnancy.—The belief has been held that even in normal pregnancy kidney function is in some way altered. This view has been

based on the probably erroneous interpretation of the well-known tendency of pregnant women to retain salt and water, and on their alleged susceptibility to proteinuria. For this reason studies of kidney function in normal pregnancy have always been considered important.

Additional interest in the renal physiology of normal pregnancy has been awakened by the recent discovery that the steroid sex hormones are capable of affecting kidney structure. Selye⁴⁰ and others^{29, 32, 36} have noted that testosterone, as well as the estrogens and progesterone, produces characteristic enlargement of the proximal convoluted tubules in the mouse. If such alterations are effected in laboratory animals by the artificial administration of these substances, it seems not improbable that the high concentrations of the estrogens and progesterone, which are characteristic of normal human pregnancy, could produce effects on the kidney that might be reflected in measurable functional changes.

Our studies on normal women include 20 patients investigated in the last weeks of pregnancy and 10 women restudied after delivery.⁵⁶ Kidney function, as revealed by these tests, was found to be unaltered by normal pregnancy or by parturition (Table I). The hormones of the placenta in the concentrations found in normal pregnancy are evidently not capable of affecting filtration rate (inulin clearance), effective renal blood flow (diodrast clearance), or the amount of functioning tubular tissue (diodrast Tm).

TABLE I. AVERAGE ANTE-PARTUM AND POST-PARTUM VALUES ON NORMAL WOMEN*

	PLASMA CLEARANCES			EFFECTIVE RENAL BLOOD FLOW C.C. PER MINUTE	INULIN/ PHENOL RED RATIO PER CENT	FILTRA- TION FRACTION INULIN/ DIODRAST RATIO PER CENT	PHENOL RED/ DI- ODRAST RATIO PER CENT	DIODRAST Tm MG. IODINE PER MINUTE
	INULIN C.C. PER MINUTE	PHENOL RED C.C. PER MINUTE	DI- ODRAST C.C. PER MINUTE					
Ante-partum	124	371	631	970	33.4	19.6	61.6	45.6
Post-partum	116	362	525	858	32.0	20.8	68.9	46.6

*The ante-partum averages are made up from observations on 20 women with inulin and phenol red clearances, 11 with diodrast clearance and 8 with diodrast Tm.

The post-partum averages are made up from observations on 10 women with inulin and phenol red clearances and 6 with diodrast clearance and diodrast Tm.

All figures are corrected to a surface area of 1.73 sq. m.

Patients With Specific Toxemia.—A total of 14 pregnancies complicated by specific toxemia have been studied in 13 patients.⁵⁵ In all of these, inulin and phenol red clearances were done, and diodrast clearances and diodrast Tm determinations were added in 11. In all of these patients records were available to show that they had no edema, proteinuria, or hypertension before the sixth month, but all had developed these signs before they were studied as toxemia patients. The

group has been divided into those patients who made a complete clinical recovery after delivery, and those in whom hypertension persisted.

The diodrast Tm (total functioning tubular tissue) was unaffected in any of the toxemia cases either before or after delivery, except in one patient discussed in a previous paper.⁵⁵

A. Toxemia of Pregnancy With Persistent Hypertension After Delivery.—There were 6 patients in whom hypertension persisted after delivery (Table II). The ante-partum clearance figures for certain patients were within the normal range. When, however, the average ante-partum figures for the whole group are compared with accepted

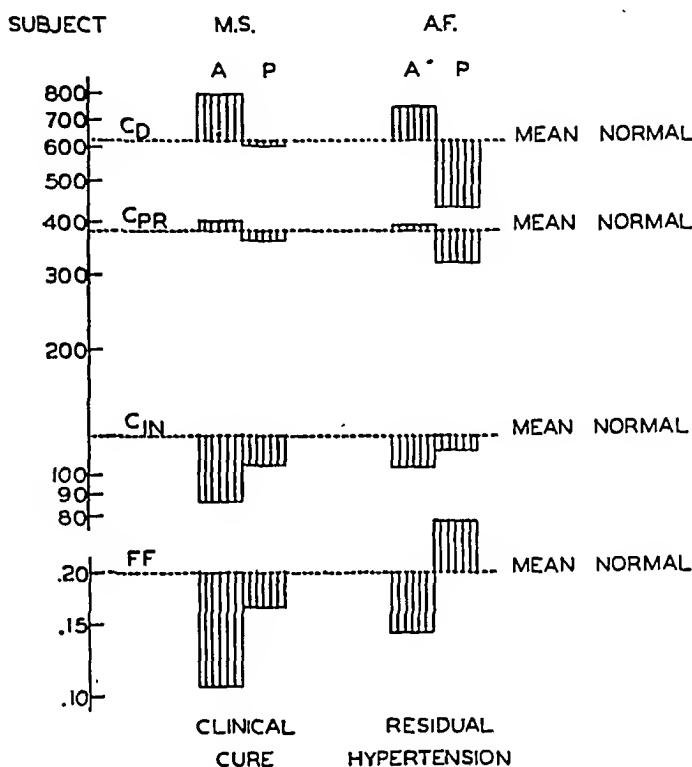


Fig. 1.—Renal clearances before and after delivery in two cases of toxemia with contrasted post-partum courses.

values for normal women or when the ante-partum figures in individual patients are compared with their own post-partum values, trends appeared which seemed to be characteristic of toxemia. These consist in a slightly reduced filtration rate, an effective renal blood flow at or above the normal value and a consequently normal or slightly reduced filtration fraction. After delivery, the filtration rate rose and the effective renal blood flow fell nearly one-third, resulting in a high filtration fraction. These post-partum findings are similar to those which have been found to be characteristic of essential hypertension.^{20, 22}

B. Toxemia of Pregnancy With Clinical Recovery After Delivery.—In 7 pregnancies complicated by toxemia, there was a complete disappearance of hypertension after delivery (Table III). The ante-partum findings were identical with those of the preceding group. Before de-

TABLE II. AVERAGE ANTE-PARTUM AND POST-PARTUM VALUES ON SIX PATIENTS HAVING TOXEMIA OF PREGNANCY WITH LATER PERSISTENT HYPERTENSION*

SUBJECT	AVERAGE NUMBER OF TESTS AVERAGED	ANTE PARTUM OR POST PARTUM	PLASMA CLEARANCES			EFFECTIVE RENAL BLOOD FLOW C.C. PER MINUTE	INULIN/ PHENOL RED RATIO PER CENT	FILTRATION FRACTION INULIN/ DIODRAST RATIO PER CENT	PHENOL RED/ DIODRAST RATIO PER CENT	DIODRAST Tm MG. IODINE PER MINUTE
			INULIN C.C. PER MINUTE	PHENOL RED C.C. PER MINUTE	DIODRAST C.C. PER MINUTE					
G. C.	1	A.	62	228			27.2			
	1	P.	118	290			40.7			
M. C.	3	A.	45	177	241	395	25.5	18.7	73.5	31.5
	1	P.	96	259	333	503	37.1	28.8	77.8	48.4
H. F.	3	A.	133	420	787	1,295	31.7	16.9	53.4	42.6
	2	P.	123	324	545	920	38.0	22.6	59.5	39.5
M. S.	2	A.	87	279	508	772	31.2	17.1	54.9	36.2
	1	P.	92	237	384	652	38.8	24.0	61.7	
H. S.	2	A.	114	354	579	882	32.2	19.7	61.2	41.2
	1	P.	119	299	448	666	39.8	26.6	66.7	
A. F.	1	A.	105	391	743	1,135	26.9	14.1	52.6	54.2
	1	P.	115	318	431	645	36.2	26.7	73.8	46.4

*Each clearance figure is the average of at least three urine collection periods per test, each diodrast Tm figure the average of five urine collection periods per test.

Columns 4, 5, 6, 7, and 11 are corrected to surface area of 1.73 sq. m.

TABLE III. AVERAGE ANTE-PARTUM AND POST-PARTUM VALUES ON SEVEN PATIENTS HAVING TOXEMIA OF PREGNANCY WITH LATER CLINICAL CURE*

SUBJECTS	NUMBER OF TESTS AVERAGED	ANTE PARTUM OR POST PARTUM	PLASMA CLEARANCES			EFFECTIVE RENAL BLOOD FLOW C.C. PER MINUTE	INULIN/ PHENOL RED RATIO PER CENT	FILTRATION FRACTION INULIN/ DIODRAST RATIO PER CENT	PHENOL RED/ DIODRAST RATIO PER CENT	DIODRAST Tm MG. IODINE PER MINUTE
			INULIN C.C. PER MINUTE	PHENOL RED C.C. PER MINUTE	DIODRAST C.C. PER MINUTE					
M. L.	2	A.	117	403			29.0			
	1	P.	118	369			32.0			
M. C.	1	A.	85	268			31.7			
	2	P.	93	333			27.9			
M. A.	1	A.	85	266	458	790	32.0	18.6	58.1	
	2	P.	118	298	547	851	39.6	21.6	54.5	36.1
M. S.	3	A.	87	400	795	1,236	21.8	10.9	50.3	
	3	P.	107	361	604	945	29.7	17.7	59.8	43.3
E. S. I	1	A.	155	523	776	1,257	29.6	20.0	67.4	68.2
	2	P.	140	411	585	957	34.1	29.9	70.3	64.7
E. S. II	1	A.	153	476	765	1,290	32.2	20.0	62.2	61.0
	1	P.	176	534	738	1,175	33.0	23.9	72.4	70.0
F. P.	3	A.	88	380	623	1,023	23.2	14.1	61.0	44.8
	1	P.	117	377	540	787	31.0	21.7	69.8	46.0
F. S.	1	A.	100	407	668	940	24.6	15.0	60.9	49.7
	1	P.	92	337	468	770	27.3	19.7	72.1	55.1

*Each clearance figure is the average of at least three urine collection periods per test; each diodrast Tm figure the average of five urine collection periods per test. Columns 4, 5, 6, 7 and 11 are corrected to a surface area of 1.73 sq. m.

livery there was a filtration rate which fell within the normal range, but was low compared to post-partum values in the same patients. The ante-partum effective renal blood flow was normal or slightly above normal. After delivery the first test showed that the filtration fraction had risen slightly, because of a small decrease in the effective renal blood flow or a small increase in filtration rate or both, regardless of whether the blood pressure had fallen to normal or not.

The characteristic changes which take place in the renal function of toxemic patients during pregnancy and after delivery are shown in Fig. 1, which is based on the tests of two patients (M. S. and A. F.) who exhibited contrasted post-partum blood pressure behavior. In this figure the dotted lines represent the mean normal values for diodrast clearance (plasma flow), phenol red clearance, inulin clearance (glomerular filtration), and filtration fraction, respectively. The blocks shaded by vertical lines represent the degree of deviation above or below the normal in ante-partum (A) and post-partum (B) values for each case. For the diodrast clearance it will be noted that in each case the ante-partum figure was a little high, while the post-partum value indicated a return to normal plasma flow in the cured patient, and a drop to a level of relative renal ischemia in the patient with persistent hypertension. The alterations in phenol red clearance followed those for diodrast, although the decrease in phenol red clearance is somewhat less. The inulin clearance ante partum was a little low when compared to the post-partum figures as obtained for each case. In both patients the filtration fraction rose with delivery, becoming somewhat above normal in the patient with the persistent hypertension.

DISCUSSION

The interpretation of these findings in terms of pathologic change in the kidney may be somewhat tentatively considered.

1. *The diminished filtration rate* found in toxemia before delivery may be explained on the basis of three possible theories or a combination of them.

a. A thickening of the basement membrane of the capillary tufts might reduce their permeability to water and cause a fall in the filtration rate. Such an explanation would be in accord with the most consistently reported histologic changes found in the kidneys of women dying of eclampsia.^{1, 2, 16, 17, 28, 31} These characteristic lesions, as already noted, consist in an enlargement of the whole glomerular tuft and a thickening of the basement membrane of the capillaries with a slight proliferation of the endothelium.

b. A second possibility to account for the diminished filtration rate, might be found in an increased intracapsular pressure which would oppose glomerular filtration. This might conceivably be produced by edema of the interstitial renal tissues. Retention of fluid is characteristic of even normal pregnancy and were this in part concentrated within the kidney, conditions would be favorable for a reduction in filtration rate.

e. Finally, the slightly reduced filtration rate in toxemia might be explained by a spasm of the afferent arteriole to the glomerulus, which would produce this effect by reducing the filtration pressure. Lesions of the afferent arteriole in eclampsia have been described and stoutly defended by Fahr,^{16, 17} and have also been reported by Irving.²⁶

2. *The normal or slightly increased effective renal blood flow* observed during the acute phase of toxemia in the presence of increased blood pressure, is an observation of considerable general physiologic interest. The fact that after delivery the renal blood flow falls before the blood pressure falls is evidence that the renal blood flow in patients with specific toxemia is not determined solely by the systemic arterial pressure and must depend on disturbance in the renal vessels themselves. As a possible explanation, it may be suggested that the observed antepartum renal blood flow and filtration fractions are the result of a slight dilatation of the efferent arterioles.

Following delivery the observations on renal blood flow and filtration fractions suggest that in the cured group there is normal efferent arteriolar tone and in the hypertension group efferent arteriolar hypertonus. The constriction of this arteriole results in a reduction of blood flow, but the raised intracapillary pressure within the glomerulus maintains the filtration rate at the normal figure.

The contribution of these functional studies to an explanation of the three cardinal symptoms of toxemia, edema, proteinuria, and hypertension is also of interest.

a. The fluid retention of normal pregnancy has been previously ascribed to the sodium retaining properties of the estrogens.⁵¹ The edema of toxemia may, at least in part, be attributable to the reduced filtration rate found in some of the toxemia cases, superimposed upon the tendency of pregnant women to retain salt and water. The immediate loss of edema fluid post partum could then be explained by the combined effects of the disappearance of the estrogens and the return of the rate of glomerular filtration to normal.

b. The proteinuria must be ascribed to an increased permeability of the capillary wall. Although this increased permeability to protein may appear inconsistent in the presence of a diminished filtration rate for inulin, the marked loss of protein in the patients with the nephrotic syndrome is also not associated with a disturbance in filtration rate.⁵³

c. Essential hypertension is sometimes ascribed to a reduced renal blood supply. Yet in the acute phase of the toxemias, as reported here, the renal blood flow is consistently normal or actually increased. The cause of the hypertension in toxemia of pregnancy cannot then be explained on the basis of reduction of renal blood supply. This finding of a normal effective renal blood flow or even a renal hyperemia in the

presence of the hypertension of toxemia is evidence against the view that renal ischemia is the primary cause of the hypertension in the non-pregnant.

Efferent arteriolar spasm and reduced renal blood flow of varying degree are typically present in essential hypertension.^{20, 22} These conditions are also present after delivery in patients who have had toxemia and whose hypertension has persisted. It is therefore probable that the residual disease of the posttoxemic patient is identical with that of the individual with essential hypertension. This view is borne out by the studies of many observers that pre-eclampsia or eclampsia may be followed by a disease which is clinically indistinguishable from the so-called essential hypertension.^{8, 15, 24, 25, 35, 52}

The fact that in toxemic patients who are going to develop persistent hypertension, there is found a high renal blood flow ante partum and that efferent arteriolar spasm and renal ischemia make their appearance within a few days after delivery suggests that factors are present during pregnancy which protect the kidney from the ischemia otherwise characteristic of the hypertensive state. Support for this view may be found in experiments reported from other laboratories. In animals in which experimental hypertension has been produced by reduction of the blood flow to the kidney, systemic blood pressure may even be reduced by the advent of pregnancy.^{10, 19, 23} It has likewise been noted in animals in which the reduction in renal blood supply was carried out during pregnancy, that the rise in blood pressure was in some instances delayed until after parturition.¹³

These studies do not demonstrate that the kidney plays a predominant role in the production of the toxemia of pregnancy. The functional disturbances observed are slight in degree, especially when compared with those seen in cases of essential hypertension or those in glomerulonephritis. They may perhaps more logically be regarded as evidence of the kidney's participation in some general vascular disturbance, than as signs pointing to the kidney as the primary source of the disease itself.

Similarly, the hypertension which follows the toxemic pregnancy must still be thought of as having an undetermined relationship to the original pre-eclampsia. One school of thought may consider that both the toxemia and the subsequent hypertension are manifestations of the same vascular disease, while another may regard the toxemia as an acute, almost accidental, process producing general vascular or perhaps specific injury of the renal arterioles, which in turn lead directly to the later phase of essential hypertension.

CONCLUSIONS

1. In normal pregnancy the glomerular filtration rate, effective renal blood flow and tubular excretory function are normal as determined by

inulin, phenol red, and diodrast clearances and diodrast Tm. There is no evidence that in uncomplicated pregnancy kidney function is in any way affected.

2. In toxemia there is a slight reduction in filtration rate, when comparison is made with the post-partum values in the same patients, an adequate renal blood flow or actual renal hyperemia, and a slightly reduced filtration fraction. These conditions afford a striking contrast to the findings in essential hypertension in nonpregnant individuals.

3. With clinical cure after delivery, there are a rise in filtration rate, a fall in effective renal blood flow and a rise in the filtration fraction, so that these values are all in the normal range.

4. With persistent hypertension after delivery, there is a considerable reduction in effective renal blood flow, and the filtration fraction becomes high. This picture of efferent arteriolar spasm and renal ischemia is like that characteristically found in essential hypertension.

5. The high effective renal blood flow found in association with the increased arterial blood pressure of the acute phase of toxemia is evidence against the view that renal ischemia is the primary cause of hypertension.

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DISCUSSION

DR. ALVIN J. B. TILLMAN (by invitation).—The clinical nature of the toxemias with the explosive appearance of albuminuria and edema, and the more recently appreciated hypertension, early drew attention to the kidney. As methods of kidney investigation changed and developed, each in turn was applied to the kidney of pregnancy. When, finally, adequate methods for determination of blood constituents were available it was felt that the answer would probably soon be found. Yet after two decades of competent investigation we have been left with a paucity of abnormal findings in blood chemistry in the toxemias. These facts have been accepted as characteristic of the toxemias, but adequate explanations as to why this disparity occurs in the face of apparent renal insufficiency have never been forthcoming. Tonight, however, we have been given a glimpse at a mechanism, of which the blood and urine findings are only reflections.

Many of us have thought that in view of: (1) spasticity of retinal vessels and capillary nail beds; (2) sudden onset of hypertension in the absence of demonstrable renal lesion; and (3) disappearance of these findings post partum, a functional ischemia of the kidney was present. There was also some thought that renal ischemia might fit in with experimental hypertension. Unfortunately for this logical thesis, these reported studies have now made it untenable.

There have been numerous studies to show the aftermath of toxemias. This later condition has been interpreted as vascular disease and as chronic nephritis. At the Sloane Hospital for Women we have considered that toxemias are followed by hypertensive vascular disease in a large percentage of cases. This belief has resulted from follow-up studies and autopsy material.

Essential hypertension results in renal change, as well as changes in other organs, but it is only after marked involvement of the kidneys that it has been possible to demonstrate these changes before autopsy. The studies of Homer Smith have made it possible to demonstrate renal change in essential hypertension. These changes, as tonight's paper has shown, characteristically occur after toxemia of pregnancy in a special group of cases.

I believe that this work, about which we have heard tonight, marks a new era in the investigation of toxemias of pregnancy.

LEON C. CHESLEY (by invitation).—You might be interested in some unusual figures derived from data of the kind which have been presented tonight. The renal blood flow in woman averages about 900 ml. per minute, and in man about 1,150 ml. per minute. This is about $\frac{1}{4}$ of the cardiac output, supplying an organ making up less than $\frac{1}{2}$ of 1 per cent of the body weight. If we add to this the liter per minute of blood which goes to the brain, we see that all of the rest of the body gets less than 45 per cent of the cardiac output. Citation of the fact that 2 per cent of the body gets well over half of the blood sounds like a socialist's statistics on the distribution of wealth.

Reckoning the renal blood flow in terms of weight per twenty-four hours, we find that in women the kidneys are perfused by 3,000 pounds of blood every day; in men this figure becomes 2 tons per day. As clinicians, you undoubtedly have answers for the patient's question as to why she has backaches, but in ease of uncertainty perhaps one might quiet the patient with something about the ton-and-a-half load of blood flowing through the kidneys every day.

The only point on which our data are not in perfect accord with those of Dr. Taylor concerns the filtration fraction in posttoxicemic hypertension, and even on this

TABLE I. RENAL HEMODYNAMICS. AVERAGE FINDINGS IN A SERIES OF WOMEN

CASES	GLOMERULAR FILTRATION ML./MIN.	PLASMA FLOW ML./MIN.	FILTRATION FRACTION PER CENT	RENAL BLOOD FLOW ML./MIN.	DEFICIT IN BLOOD FLOW PER CENT
<i>Normal Women</i>					
30	116	567	20.4	850	0
<i>"Male Type" Essential Hypertension</i>					
11	106	351	30.2	559	34
<i>Posttoxicemic Hypertension</i>					
16	85	408	20.8	640	25
<i>Posttoxicemic, Normal Blood Pressure</i>					
6	97	526	18.8	774	10

we are not too far apart. In Table I, I have summarized some of our findings. Our glomerular filtrations have been approximated from maximal urea clearances, which are assumed to be 60 per cent of the filtration level. In individual cases this entails some error, but our average filtration rate comes out as 116 ml. per minute, as compared with Dr. Taylor's measured value of 119 ml. per minute. Our calculated filtration fraction averages 20.4 per cent for normal women, and is unaffected by pregnancy; Dr. Taylor's value is 20.0 per cent.

In a group of hypertensive women who have never had a pregnancy, or at least never had a toxemia, the filtration fraction is considerably elevated, averaging 30.2 per cent. There is an associated reduction in renal blood flow. These findings are explained by constriction of the efferent arterioles which, as Dr. Taylor has said, is characteristic of essential hypertension.

When we examine the posttoxicemic hypertensive patients at six weeks to four years post partum, we find that the filtration fraction is usually normal, so that the reduction in renal blood flow is paralleled by a reduction in the filtration. Of 16 cases, only 3 (or $\frac{1}{5}$) have filtration fractions above 25 per cent. Corcoran and Page measured the renal blood flow and glomerular filtration in 5 patients with posttoxicemic hypertension; 2 had filtration fractions of 22 per cent, 2 of 23 per cent, and 1 of 27 per cent, again only one-fifth with significantly increased filtration fractions. Their patients were from four weeks to three years post partum.

Whatever the significance of the observation may be, posttoxicemic hypertension can often be differentiated from the "male type" of essential hypertension by the simultaneous measurement of the clearances of diodrast and urea. Since we consider the urea clearance as a proportional measure of glomerular filtration, subject to errors, the differentiation is based upon the filtration fractions. I believe that this finding has an important theoretical significance, and I should like your leave to speculate upon it for a few minutes.

The lesion most constantly found in women dying of acute toxemia is the one stressed by Dr. Taylor, a diminution in the lumina of the glomerular capillaries. Whether or not this lesion persists during the months and years after toxemia is an open question. Bell, Page and Cox have described such persistent lesions in the glomeruli of 8 women dying from intercurrent causes some time after toxemia. On the other hand, Baird and Dunn, and Keller failed to find the lesion in the kidneys of 4 women dying of recurrent toxemia. In the absence of more extensive and more concordant anatomic observation, we have attempted a "chemical dissection" of the posttoxicemic kidney, using the clearance methods.

If the glomerular capillaries are persistently narrowed after toxemia, then one might expect to find a somewhat diminished renal blood flow, and a nearly parallel reduction in glomerular filtration; the filtration fraction would be nearly normal, since pressure in the capillaries would not be much changed. These are exactly our findings.

This finding has a bearing upon the question of whether the toxemia causes the later hypertension, or is merely a sign that the patient is eventually to have hypertension regardless of the toxemia.

The probable mechanism of renal hypertension is shown in Table II. As Dr. Taylor has remarked, renal ischemia is probably a secondary effect rather than a cause of hypertension. Even slight narrowing of the capillary lumina would considerably increase the resistance to perfusion, which would be reflected by an increase in the intrarenal diastolic pressure. The systolic pressure remains at the usual levels, the intrarenal pulse pressure must be reduced, and thus the cycle would be initiated, and hypertension result.

TABLE II. PROBABLE MECHANISM OF RENAL HYPERTENSION

(Simplified from data of I. H. Page)

-
1. Reduction in intrarenal pulse pressure.
 2. Release of renin from kidney.
 3. Activation of renin → angiotonin.
 4. Generalized arteriolar constriction, *especially marked in the efferent glomerular arterioles.*
 5. Further reduction in the intrarenal pulse pressure, thus establishing a vicious cycle.
-

TABLE III. CONTRAST BETWEEN RENAL AND POSTTOXEMIC HYPERTENSION

Characteristic findings in renal hypertension:

1. Diminished renal blood flow (renal ischemia)
2. Increased filtration fraction (because of efferent arteriolar constriction)

Findings in posttoxemic hypertension:

1. Diminished renal blood flow (usually)
 2. Normal filtration fraction
 - (A) Are the efferent arterioles not constricted?
 - (B) Are the efferent arterioles constricted but the effect masked by decreased glomerular permeability?
-

But these cases of posttoxemic hypertension do not appear to fulfill the criteria for renal hypertension, because of the normal or only slightly increased filtration fractions (Table III). Perhaps this can be explained on the basis of decreased capillary permeability, which we have suggested as a possible explanation for the reduced filtration found during the acute toxemia. The high intracapillary pressure caused by the efferent arteriolar constriction may be expended in maintaining a normal filtration fraction. Thus the efferent spasm would be masked by the decreased capillary permeability.

If it is presumed that a lowered filtration fraction during toxemia is the functional manifestation of glomerular damage, and that posttoxemic hypertension is caused by persistence of that damage, then those women with the lower filtration fractions should show a higher incidence of later hypertension. Of 16 patients with normal filtration fractions during the toxemia, only 1 now has hypertension, and she has had another toxemia. Among the 10 patients with decreased filtration fractions, 4 have hypertension at two years after the toxemia. Four other patients had efferent constriction at the time of their pregnancies. Three of these were not true toxemias, in that hypertension had antedated pregnancy, and is still present; in the fourth case, the mild pre-eclampsia was complicated by a pyelitis which may have disturbed the renal hemodynamics.

DR. JAMES SHANNON (by invitation).—A striking feature of Dr. Taylor's data is the small difference between the normal and the patient with a specific toxemia. The lowering of glomerular filtration rate seems to be a regular finding. However, this is scarcely extensive enough to account for the disturbance in water and electrolyte balance even if one assumes that the retention of sodium is enhanced by excessive amounts of salt-retaining hormones. This raises the question of whether the tests as carried out at the present time are adequate evaluations of the functions of the kidney which are of importance in precipitating or conditioning the specific toxemias.

In the presence of a normal circulation and normal antidiuretic activity, the renal control of the volume of extracellular fluid is through the rate of glomerular filtration, and hence the filtration of sodium, and the ability of the proximal tubule to

reabsorb sodium. The latter is, of course, influenced dramatically by several hormones. Normally the individual retains or excretes sodium by varying one or another of these factors. Some hours after a meal containing salt a precise balance will be struck between the filtration and reabsorption of sodium so that a constant amount of sodium is retained in the body. We have information on how this balance is struck in the dog. Here, the glomerular filtration rate varies and is responsible for maintaining the system in its normal state. I suspect this may also be true in normal man. If this suspicion is correct then a man is not normal because of an absolute value for the rate of glomerular filtration but because the filtration rate can respond adequately and promptly to return the system to normal. By selecting sixteen hours after the last meal as the time for observations and obtaining these at complete rest, the reactivity or nonreactivity of this function will not be uncovered. This could be determined if having obtained control observations, as in Dr. Taylor's experiments, the system were then disturbed by the administration of physiologic saline. Information from such experiments would base the judgment of the normality of filtration rate both on a numerical value for this obtained at rest and upon the degree of reactivity uncovered in the experiment.

These considerations do not minimize the contribution of tonight's paper. However, considering the next step in the study, the necessity of obtaining a dynamic picture of the condition is apparent. I have stressed the electrolyte phase of the problem because it seems likely that when one feature of the symptom complex has been clarified from the standpoint of the mechanisms involved, others will fall in line. And with our present knowledge of the kidney, it is probably simpler to manipulate the electrolytes than some of the other more complex phases of renal function.

DR. R. GORDON DOUGLAS.—For some time we have been carrying out some of these examinations, both as far as glomerular filtration and renal blood flow are concerned. We have at the moment a patient in the pavilion who, following several tests, appears to have an unusually large renal blood flow with a clinical diagnosis of mild pre-eclampsia. The picture does not quite fit into some of the observations made this evening, nor does it fit in with some of the observations that we have made formerly.

From a purely practical point of view, I do not see how we can change our diagnostic or therapeutic measures in the care of pre-eclampsia and hypertensive disease. I think it is interesting to note that Corcoran and Page have attempted, after carrying out these tests on a relatively small number of patients, to differentiate mild pre-eclampsia, pre-eclampsia and hypertensive disease. It appears to me that their conclusions in this respect are hardly justified on the basis of the data that they have presented to date.

Möller-Christensen, E., and Thorup, Chr.: Vitamin C Content of Umbilical Cord Blood, Maternal Blood and Colostrum, *Zentralbl. f. Gynäk.* 64: 1858, 1940.

The authors studied vitamin C content in 10 labor cases. A consistent gradient appeared in which placental tissue contained the highest percentage of ascorbic acid, maternal blood the lowest. Average figures in mg. ascorbic acid per cent were: maternal blood 0.44 mg. per cent, colostrum 0.80, cord blood 1.06, and placenta 10.10. Technique of the determinations is given.

R. J. WEISSMAN.

GRANULOSA CELL TUMOR OF THE OVARY AND COINCIDENT CARCINOMA OF THE UTERUS

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(From the Department of Pathology of the Woman's Hospital)

DURING the past two decades investigations in the field of carcinogenesis developed considerable information, which indicates that cancer may be induced by a number of different factors. The approach to this problem was twofold: First, clinical observations that identical malignant tissue growth may occur in the human being, when groups of individuals are subjected to certain environmental conditions; second, experiments which resulted in the production of tumor growth in laboratory animals.

To those factors, operating by chemical, physical, and biologic action, which proved conducive to tumor growth, the collective name of "Carcinogens" was applied, since they stimulate predominantly the epithelial tissues to proliferate. The incessant work in the field of carcinogenesis, mainly conducted by biochemists, centers in the discovery that the chemical carcinogenic agents are polycyclic hydrocarbons, which, by their chemical structure, are correlated to the sex hormones (sex sterols). Thus a common chemical background of these carcinogenic factors and the sex hormones was established.¹

The physiologic manifestation of the growth-stimulating effect of the female sex hormone is expressed by periodic phases of proliferation and of subsequent regression in the tissues of the female sex organs due to the coordinated action of these hormones.

The question whether such growth-stimulating substances, when unopposed, might produce unlimited (malignant) tissue-growth rose from the observation that the female genital tract occupies the first place among all other organs as the site of malignant tumor development, giving rise to 21 per cent of all tumors in the human female.

Basic evidence of the stimulating effect of the ovary toward carcinogenesis in the mamma of rodents was produced by the experiments of Loeb,² Lacassagne,³ Gardner⁴ and others. They conclusively demonstrate that the carcinogenic effect of estrogenic substances is proportionate to the amount administered, that, due to certain intrinsic biologic factors, some strains of the same species are tumor-resistant and that different synthetic estrogens vary in carcinogenic potency in proportion to their physiologic activity.

The uterus, as the physiologic site of predilection for the effect of the ovarian hormones, was found less responsive to tumor formation by estrogenic stimulation in animal experiments. Most remarkable is the infrequent occurrence of uterine tumors in rodents, considering the comparatively colossal procreative activity of this species and the high frequency of breast and ovarian tumors.

Therefore, experimentally produced epithelial alterations and tumors in the uterus are of great importance for the problem of carcinogenesis by hormonal activity.⁵⁻¹² The effect of large amounts of estrogens was studied in mice, rats, rabbits, guinea pigs, and monkeys in numerous experiments which are consistent in the result that in the uterus excessive administration of estrogens is manifested by:

- a. Hyperplastic proliferation of the glandular structures of corpus and cervix.
- b. Malignant overgrowth of the epithelium in the form of carcinoma-like and true carcinoma development.
- c. Metaplastic alteration of the epithelium.
- d. Hypertrophic development of stroma and muscle tissue.
- e. Tumor growth of stroma and muscle tissue.
- f. Aseptic suppurative necrosis.

The epithelium of the cervix and of the vagina presents itself as the more favorable tissue of response to excessive growth by estrogenic stimulation. The fundus of the uterus of monkeys is entirely refractory to estrogenic tumorigenesis; spontaneous tumor development here has not been observed.

Investigations agree that in the uterus a tumor-inciting effect by ovarian hormones is missing, contrary to the experimental result in hormonal carcinogenesis in the breast. "Estrogenic hormones evidently induce the development of carcinoma in those organs in which they call forth long-continued or often-repeated growth processes."¹³

Another approach to the problem of experimental production of tumor growth on hormonal basis was initiated by the work of Furth and Furth,¹⁴ who produced results on the increase of tumor incidence in experimental mice treated with x-ray radiation.¹⁵ From these findings it appears that the incidence of ovarian tumors in irradiated mice was fifteen times more frequent than in nonirradiated mice. These tumors are essentially represented by two forms: those cytologically related to the granulosa cell tumor and those simulating the tubular adenoma.

It is important to note that hormone production by these tumors is manifested by the correlation between these experimental tumors and co-existing breast tumors. While in 374 irradiated mice of a tumor-susceptible strain without ovarian tumors, only 2.7 per cent breast tumors were observed; in 57 identically treated mice with ovarian tumors, breast neoplasms were co-existent in 21 per cent. These observations become still more impressive when applied to a group of 42 mice, bearers of granulosa cell tumors, in which 28.6 per cent developed breast tumors, while in 15 mice with tubular adenoma no breast tumor was observed.

Estrogen production by these artificially produced tumors, as evidenced by the vaginal cycle, could be proved in the presence of granulosa cell tumor and the luteoma and not in the presence of the tubular adenoma; findings which correspond to conditions in the human female.

The granulosa cell tumor in the human being appears in a variety of histologic patterns of mature and immature character. Notwithstanding their morphology they impart upon the bearer a syndrome of biologic changes due to the active production of female sex hormone characterized by growth in the tissues of the reproductive organs.

The most frequent evidence of the growth-stimulating effect of these neoplasms is the excessive proliferation of the uterine mucosa which

is the criterion for estrogen elaboration and is identical in its diagnostic value with the keratinization phenomenon of the vaginal mucosa in the rodents. Thus, its presence indicates the evidence of the hormone-producing activity of the granulosa cell tumors in the human. Proof of this was rendered by various methods, by biologic assays,¹⁶⁻²¹ by tumor extracts,^{22, 23} and by tumor grafts.^{16, 18, 24, 25} The latter form of experimental proof for natural reasons had to remain confined to animals.

Although the literature is abundant in reports on granulosa cell tumors in the human being, the biologic demonstration of their estrogen-productive activity is surprisingly sparse.²⁶ The reason might be that the clinical diagnosis of the granulosa cell tumor is infrequent and is established for the most part postoperatively at a time when the hormone level in the patient is decreased or has been restored to the normal.

The figures resulting from biochemical examinations vary considerably in the different cases. The most extensive investigations were performed by Schuschania¹⁷ who assayed in the human subject the daily hormone output in the urine and feces before and after operation, whereby findings as high as 195 M.U. in the urine and 123 M.U. in the stool were obtained preoperatively.

Extracts of tumor tissue gave less remarkable results. Neumann obtained 4 M.U. from 84 Gm. of tumor and 1 M.U. from 5 c.c. of blood drawn from a venous vessel of a tumor proper.

The least satisfactory results were obtained by direct implantation of tumor tissue. Most investigators report completely negative results, a fact possibly explained by the technical difficulty of implanting adequately large quantities of tissue.

From these and other investigations referred to above and in view of the carcinogenic potency of estrogens in animals, it may be inferred that the granulosa cell tumor, as the source of continuous estrogen production, may lead also in the human subject to unlimited and eventually malignant growth of those tissues which physiologically are subordinated to this hormone.

The correlation between the benign glandular hyperplasia and the malignant form of growth was shown with more convincing evidence in the endometrium than in other organs. The frequency of their co-existence has given weight to the belief that the benign hyperplastic form may undergo transformation into the malignant form by a slow growth process.

The following case reports are intended as further proof (1) of the carcinogenic potency of the granulosa cell tumor in the human individual by virtue of its hormonal activity, and (2) to indicate the potentiality of the histologically benign pattern of glandular hyperplasia of the endometrium to undergo malignant proliferation.

CASE 1.—(No. 48752.) Patient, aged 64, para vi, menopause 7 years ago, had slight excessive bleeding before onset of menopause, moderate

metrorrhagia for past two months, and enlargement of abdomen in lower right quadrant during the last seven months.

Surgery.—Removal of myomatous uterus and of both adnexa.

Specimen.—The uterus was enlarged to 11.5 by 7 by 5.5 cm., and a myoma 5 cm. in diameter was in the left horn. The endometrium of the corpus was unusually hypertrophic; the mucosa of the cervix was cystic and hypertrophic.



Fig. 1.—(Case 1.) Low-power photograph of endometrium in situ demonstrating hyperplastic and carcinomatous glands.



Fig. 2.—(Case 1.) High-power photograph of endometrium showing carcinomatous glands.

The right appendages were of atrophic appearance. The left ovary was converted into a cyst of man's head size, filled with brown thick fluid, which amounted to about 1,000 c.c. The inner surface of the cyst bore a thick coat of spongy, frayed tissue, breaking off in small particles, which were suspended in the fluid. A thickened tube was attached to the cyst by the shortened ligament.

Microscopic Findings.—The uterine mucosa composed an unusually broad layer, which projects into the lumen in polyplike fashion. It presented great variety in structure. Predominant in the picture was a dense dissemination of glands, which partly were of typical hyperplastic type, often in cystic degeneration mostly with hypertrophic epithelium. Other broad fields were occupied by giant glands, which in their most peripheral portions were greatly convoluted and which in other areas throughout their entire course were branching and contorted; where excessive proliferation and folding had taken place, solid alveoli were produced. In few spots glands and stroma projected toward the myometrium, however, without evidence of invasion. The irregularity of the architecture of the mucosa was enhanced by the unusual hypertrophy and hyperproliferation of the epithelium proper, which composed broad layers due to pseudo- and true multiplication of cell rows. Cells here revealed loss of orientation, irregular distribution, and marked aberration from the mature form. Nuclei particularly were irregularly disposed, exhibiting great variation in form and

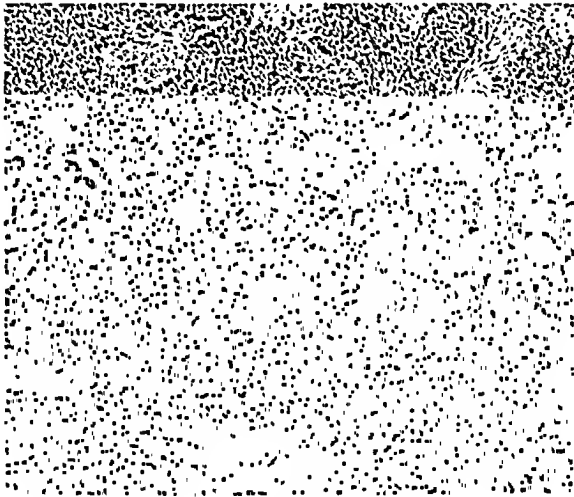


Fig. 3.—(Case 1.) Granulosa cell tumor of ovary.

size. The abundance of gland structures, their close dissemination with almost complete lack of intervening stroma, the morphologic irregularity of the glands, the excessive epithelial proliferation and its deviation from the normal designated the malignant character of the adenomatous growth.

The cervix mucosa was hypertrophic; glands here likewise were partly cystic, partly of complex build, and the epithelium was in a state of hyperproliferation.

The cystic tumor of the left ovary revealed ovarian stroma in the capsule only. The solid portion was built of a neoplasia, which presented the structure of a granulosa cell tumor of the massive form. Cells, which uniformly were of mature type, composed wide fields in massive arrangement and revealed only slight tendency to form rows and narrow trabeculae.

The right ovary revealed senile atrophy.

Both tubes presented fibrous atrophy of the mucosa and of the wall.

Diagnosis.—Myomatous uterus, adenocarcinoma of endometrium (adenoma malignum) and excessive glandular hyperplasia, granulosa cell

tumor of left ovary, senile atrophy of right ovary, and senile atrophy of both tubes.

Follow-Up.—Patient was observed for the following nine years, during which time she remained well.

CASE 2.—(Record number 60848.) Patient, aged 42 years, nullipara, menstrual history unessential, had had amenorrhea for six months prior to operation. There had been an enlargement of the abdomen for six months and pains in the left side of abdomen for past two years.

Surgery.—Curettage, removal of left ovarian tumor and part of left tube; appendectomy.

Specimen.—The specimen consisted of about 3 c.c. of soft curettings with one larger fragment among them. Tube and ovary formed a mass 13 by 9 by 7 cm.; the tube was 6 cm. long, and its diameter was 1 cm. on the average. The ovary was converted into a large, multilocular

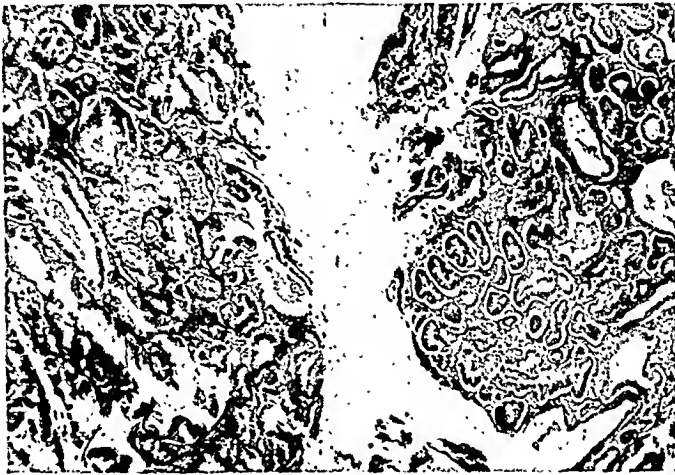


Fig. 4.—(Case 2.) Low-power photograph of endometrium (curettage), showing benign glandular hyperplasia on the right and adenoma malignum on the left.

cyst, whose wall was partly delicate, partly thick and firm, of albuginea-like appearance, and whose inner layers were composed of a medullary yellowish tissue; the latter formed cushion-shaped projections with frayed surfaces. Tissue destruction in the form of hemorrhagic necrosis was apparent in large areas. The cystic compartments were filled with hemorrhagic fluid and tissue debris. The tube had typical appearance except for the adhesions which tied it to the ovary.

Microscopic Findings.—Part of the endometrial fragments presented marked glandular hyperplasia frequently with cystic degeneration. The epithelium here showed hyperproliferation and pseudostratification; cells were uniform, of mature type, and regularly arranged.

The majority of the fragments were built differently than the above described ones. Glands were greatly varying in size; they were highly irregular in shape, many of them attained huge size; they were in dense distribution and mostly in dos-à-dos position. The epithelium was excessively proliferating, forming multiple stratified rows, folds, and tufts, yet it remained within the limits of the glands with an undisturbed basal membrane and preserved also, in those instances where proliferative activity was most pronounced, conformity with the endometrium. Thus a growth pattern is produced, which involves all char-

acteristics constituting the adenoma malignum, which in the endometrium is identical with the most mature form of the glandular carcinoma.

The constituent cells were generally of the highly differentiated type, however, markedly atrophic, with numerical increase of mitoses; where cell proliferation was most excessive, irregularity of the cell shape and of the disposition and structure of the nucleus became predominant, enhancing the morphologically malignant form of growth.



Fig. 5.—(Case 2.) High-power field occupied by adenoma malignum.



Fig. 6.—(Case 2.) Low-power photograph of a fragment of cervix-mucosa with squamous cell epithelium.

Other small fragments, which were discretely scattered among the glandular tissue fragments, were composed of typical stratified squamous epithelium and of glands, which by shape and by the type of epithelium indicated their origin from the cervix. The squamous cell epithelium formed plump cones, which partly lay freely in the stroma, or it built sinuous bands. Where it overgrew the glands, it appeared in some instances to arise from and to overlap the inner border of the columnar epithelium, whence it projected as folds and tufts into the lumina. Thus a growth pattern was apparent, which might be inter-

preted as the result of a transformation of the mucous epithelium by a metaplastic process combined with the classical hyperproliferative process of epidermization.

The cystic ovarian mass represented a granulosa cell tumor mainly of massive type, in which the more differentiated architecture of trabecular formation was only slightly developed. Some residual ovarian tissue was preserved within the capsulelike peripheral stratum.

The tube did not reveal pathologic changes.

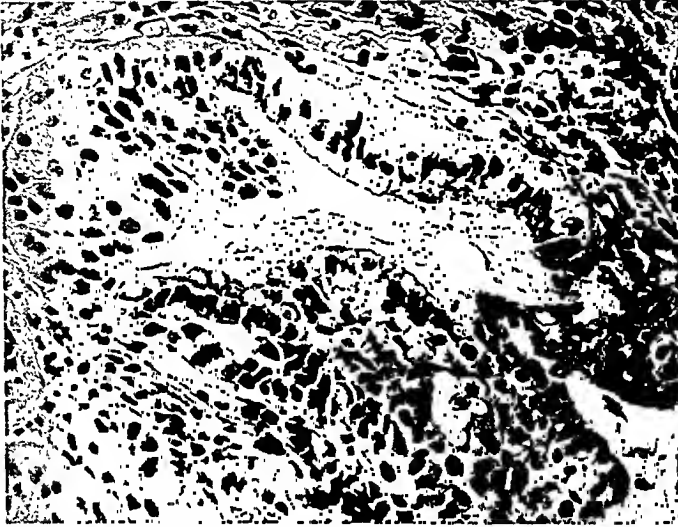


Fig. 7.—(Case 2.) High-power photograph of cervix mucosa demonstrating relation between columnar and squamous cell epithelium.

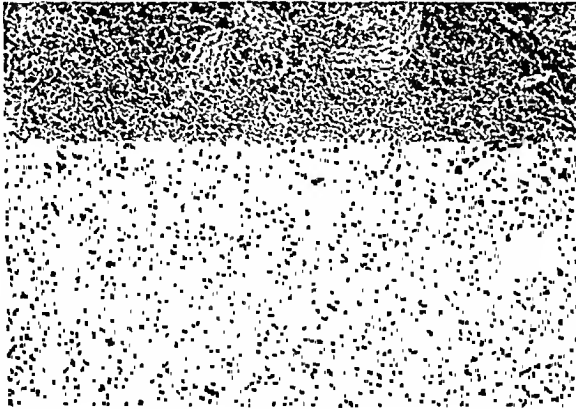


Fig. 8.—(Case 2.) Granulosa cell tumor of ovary.

Diagnosis.—Glandular hyperplasia of endometrium and adenocarcinoma, hypertrophy of squamous cell mucosa of cervix, granulosa cell tumor of ovary, and normal tube.

Normal menses were restored six weeks after operation.

In view of the neoplastic overgrowth of the endometrium, a curettage was performed eight weeks following removal of the tumor. The endometrium then presented an early secretory pattern of the most typical form coinciding exactly with the clinical phase of the cycle.

Follow-Up.—Patient was observed during the following five years; she remained well and presented a normal menstrual history.

CASE 3.—(Record No. 67687.) Patient, aged 60 years, para ii, menstrual history irrelevant, had had menopause ten years prior to operation. She had had severe metrorrhagia two months preceding and continuing up to hospitalization. Abdominal pain had been present for two weeks, and she had lost 10 pounds in weight.

Surgery.—Diagnostic curettage.

Specimen.—The specimen consisted of 3 c.c. of fairly large endometrial fragments with granular surfaces.



Fig. 9.—(Case 3.) Low-power photograph of uterine curettings showing the papillary carcinoma; on the right a fragment composed of hyperplastic, nonmalignant mucosa.

Microscopic Findings.—A large part of the material presented typical glandular hyperplasia partly with cystic degeneration of marked extent. Several of the fragments were made up of a papillary adenocarcinoma of pronounced maturity in structure and cell type. There was general marked hyperproliferation of the epithelium leading to manifold multiplication of layers and to the formation of diffuse cell masses. These formed partly solid papillary projections and partly invaded the stroma as compact aggregations. Changes in cell type were indicated by the transgression from the tall columnar cell to the transitional cell form, which in multiple instances attained gradually the character of the mature squamous epithelial cells. The latter appeared either in the peripheral layers of the papillae or they formed solid aggregations and composed the entire papillary structure.

Diagnosis.—Cystic glandular hyperplasia of endometrium and papillary adenocarcinoma of corpus uteri with extensive squamous cell metaplasia.

Therapy.—Intrauterine radiation of 2,426.88 mg. hours of radium was given. Six weeks postradiation panhysterectomy was performed as standard procedure in cases of adenocarcinoma of the corpus uteri.

Specimen.—The specimen consisted of uterus and both appendages. The uterus was enlarged in all dimensions, measuring 13 by 8 by 7 cm.;

a myoma projected. The endometrial canal bore a spongy layer in the fundus, the rest of the endometrium was atrophic; the lining of the cervical canal was hypertrophic. The uterine muscle was increased in mass considerably. Both tubes were 11 cm. long; they were thin and highly congested. The right ovary was a fibrous body 2 by 1 cm. The left ovary was converted into a thin-walled cyst 5.5 cm. in diameter with hemorrhagic structures on the inner surface.



Fig. 10.—(Case 3.) Medium high-power photograph of the carcinoma of the endometrium with transition of the columnar to the squamous cell epithelium and solid papillae of squamous cell epithelium.



Fig. 11.—(Case 3.) Granulosa cell tumor of ovary.

Microscopic Findings.—The mucosa in the fundus was well preserved in parts and represented glandular hyperplasia with epithelial overgrowth leading to multiplication of cell layers identical to the described picture in the preceding curettage. There was slight increase in pathologic mitoses. The stroma was of typical texture; it was vascular with more or less extensive round cell infiltration. In the mid-portion of the corpus canal destruction of the endometrium was ap-

parent. Where the basal portion was preserved, glands were distended and showed occasional proliferation and hypertrophy of the epithelium.

The cystic ovary of the left side proved to be a granulosa cell tumor, in which the trabecular type was predominantly represented, with numerous Call-Exner bodies scattered in the cell aggregations productive of a star-covered pattern. Irregular oval or round microscopic cysts simulated cystically degenerated ovarian follicles, in which occasionally the deceptive attempt at formation of a cumulus oophorus was apparent. The maturity of the tumor was manifested by the high differentiation of the composing cells and by their ability to reproduce characteristic formations peculiar to the granulosa cell.

The right ovary represented extensive atrophy and fibrosis.

The mucosa of both tubes was hypertrophic, the epithelium was tall, juvenile, and in a state of active proliferation; it corresponded to the type coinciding with the late proliferative phase of the cycle.

Follow-Up.—Patient remained apparently well for nineteen months. She died with the symptoms of intestinal obstruction twenty months postoperatively in another hospital. Autopsy was inconclusive as to the presence of carcinoma. Assays of the hormone output in the urine were performed on the first day following operation and four weeks later. The first examination revealed an estrogen concentration of 172 M.U. per 1,000 c.c. of urine, the second examination did not yield any determinable estrogen content in the urine. The high value of estrogen obtained in the first urine assay is well in correspondence with the maturity of the granulosa cell tumor present in this case.

DISCUSSION

The literature of the granulosa cell tumor, abundant as it is, includes only a scant number of similar cases.

Schroeder²⁸ reports one case of a mature form of the granulosa cell tumor in a woman 45 years of age, whose clinical history suggests the existence of the tumor for at least four years. The uterine mucosa shows glandular hyperplasia in general. However, several areas suggest malignant degeneration by irregularity of glandular shapes, multiplication of epithelial layers and structural and morphologic deviations of the epithelial cells.

A similar case is reported by Russell,²⁹ who describes a diffuse polypoid hyperplasia of the endometrium, approaching the extent of carcinomatous overgrowth, associated with a large granulosa cell tumor of the ovary in a woman 67 years of age. "Glands show general epithelial proliferation and in areas a degree of metaplasia resembling a carcinoma." The granulosa cell tumor is of sarcomatous, cylindromatous, and trabecular type. The clinical history of the case indicates the presence of the tumor for approximately four years.

TeLinde³⁰ reports in his series of granulosa cell tumors one case (No. 4) of simultaneous occurrence of an adenocarcinoma of the corpus uteri and an ovarian tumor of specific build, which is listed among the granulosa cell tumors by Pratt,³¹ when reviewing the literature of granulosa cell tumors at a later date. However, at the time of publication, the author left the diagnosis of this ovarian tumor undecided as the differentiation of the granulosa cell tumor from other specific ovarian tumors was then still ill-defined. As it ensues from the microscopic description and from the photomicrographs this ovarian neoplasm in all probability represents a Brenner tumor.

SUMMARY

Three cases of granulosa cell tumor of the ovary are described in which the glandular hyperplasia of the endometrium attains the character of neoplastic growth productive of a variety of malignant features.

Granulosa cell tumors are not only differentiated by their morphologic criteria but manifest themselves also by their specific biologic function, which is focused in the elaboration of estrogenic hormone and subsequently by their growth-promoting effect upon those organs which physiologically are subjected to estrogenic stimulation. Predominant among them is the uterus, which responds by muscular hypertrophy and by proliferation of the mucosa as observed in the many instances of recorded granulosa cell tumors.

In the cases described unusual responsiveness of the endometrial tissue is apparent by excess growth and by development in a malignant form conditioned by the prolonged hormone elaboration of the tumor cells. Therefore, these cases may be accepted as spontaneous biologic experiments in the human being in analogy with those growth processes experimentally induced in organs of the reproductive tract of animals, particularly in those of tumor-susceptible strains.

As observed in the study of large series of granulosa cell tumors³² the responsiveness of the endometrium to the granulosa cell tumor varies considerably in the different cases. It may be assumed that in certain individuals, like tumor susceptibility in certain animals of the same species, a specific readiness exists in the tissue cells (endometrium) to multiply in excess and in unlimited fashion, when stimulated by estrogenic substances.

Other factors, too, may be involved which, at present, can only be conjectured. These are possibly individual variations of the tumor bearer in regard to the metabolism of the sex sterols or quantitative variations of the hormone-genetic potency of the elements of the granulosa cell tumor. Here it is of importance to note that in all three cases described the cells of the tumors are of mature character reaching in the last case the highest degree of differentiation expressed by the faculty to form follicle-like structures; whereas in tumors with markedly undifferentiated cell type, as in the cases of frank granulosa cell carcinoma, atrophy of the endometrium is generally observed. Hence, it may be inferred that the closer the approach to the mature form of the granulosa cell of the Graafian follicle, the more extensive the production of the hormone and the greater the growth-inducive stimulus.

Case 2 lends unquestionable proof of the etiologic dependence of the uterine growth upon the ovarian neoplasm by evidence of the reversibility of the growth process. In conformity with the animal experiment, glandular epithelium, in the state of hypertrophic or malignant proliferation due to estrogen stimulation, may be restored to the normal status, when stimulation by the hormone ceases. In the above case

the return of regular menstrual cycles after removal of the tumor indicates restored gonadal function, as substantiated by the second curettage which yielded a normal secretory mucosa and by the further clinical course.

The unusual form of the squamous cell proliferation apparent in the fragments derived from the cervix indicates a growth process comparable to those hyperproliferative and metaplastic developments in cervix and vagina of different test animals. However, the comparison is not offered without hesitation since the material is scant and fragmented, not disclosing its relation and its mode of propagation toward the cervix proper; furthermore it has to be borne in mind that growth in excess is a common attribute in processes of repair and healing in the diseases of the cervix uteri. In conjunction with the neoplastic overgrowth in the corpus uteri, considered to be on estrogenic basis, these formations of squamous cell epithelium may be looked at from a different angle and etiologically explained as the result of the identical growth-stimulating factor.

In Case 3 an unusual form of the endometrial carcinoma is presented, mainly characterized by an active papillary growth in which cell metaplasia is the outstanding feature. The columnar cell form is in a state of transition to the squamous cell type giving rise, like a basal cell layer, to orderly stratified, mature squamous cells. The morphologic structure of the uterine growth in this case and the form of cell transformation are reminiscent of those metaplastic and precancerous changes occurring in the uteri of rats, mice, and guinea pigs after systematic estrogen administration over long periods.

The further course of this case is somewhat obscured by an inconclusive autopsy report. The patient died from intestinal obstruction short of two years after treatment. It may be considered that the granulosa cell tumor remained in situ for six weeks after radiation, was histologically unaffected and possibly stimulated by the uterine radiation, during which time gross engendering activity obviously had been maintained. The character of this endometrial tumor which in its final form of development approaches tumors of epidermal origin may be aligned with those estrogenic tumors of the skin which prove to be of autonomous and irreversible nature.

In this case the argument for a coincidental simultaneous occurrence of the ovarian and of the uterine neoplasms cannot be definitely refuted; however, the unusual character of the uterine neoplasm speaks in favor of its dependence upon the ovarian tumor and consequently upon the hormone produced by it.

Furthermore, these findings may be considered of sufficient importance to be applied to the etiologic explanation of those heterotopic cell formations which are occasionally encountered in the human being in cases of glandular hyperplasia of the corpus and cervix uteri or in the carcinoma of the uterus³³ and less frequently in the carcinoma of

the ovary.³⁴ They are shortly referred to as squamous cell metaplasia, squamous epithelial nodes and adenocarcinoid. They appear as nodular aggregations similar to immature squamous epithelial cells and seemingly represent different stages of specific cell differentiation. They may develop from extraglandular, undifferentiated cells under the influence of certain provocative factors or they may develop from the glandular epithelium in a minutely graded transitional growth process. These changes may be the result of mutative processes during successive cell generations, presumably maintained by a modifying factor. On the basis of the previously mentioned metaplastic growth processes in animals they may well be attributed to the stimulus by estrogenic substances.

The ever increasing experimental and therapeutic use of high concentrates of estrogens, as applied at present, might possibly add definite facts to these attempts at explanation of neoplastic processes which at their best remain at present only conjectural.

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ROENTGENOGRAPHY OF THE OBSTETRIC PELVIS*

A COMBINED ISOMETRIC AND STEREOSCOPIC TECHNIQUE

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ROENTGEN ray examination of the obstetric pelvis at term and during labor offers visual perception of images which can be interpreted if correction is made for distortion. This may be achieved by comparative, teleoroentgenographic, frame, triangulation, grid, isometric scale and stereoscopic techniques as discussed in the papers of Ball, Clifford, Granzow, Hodges and Dipple, Moloy, Moore, Rowden, Thoms, Walton and Snow. These methods require scales or grids, formulas, plotting paper, calculators, stereoscopes, or stereoroentgenometers. Each method has advantages and disadvantages. Of those in use in this country, the isometric scale method popularized by Thoms, and the stereoscopic technique used by Caldwell, Moloy, and D'Esopo, seem best adapted to complete survey of the obstetric pelvis.

The obstetric pelvis has been studied radiographically in the Woman's Clinic of the New York Hospital since 1934. A total of 1,300 patients have been examined. A preliminary report based on experience with the stereoscopic technique and ordinary lateral film of Caldwell and Moloy was made by Steele, Wing, and McLane in 1938. In the succeeding four years, an isometric scale has been used in the lateral film in addition to the stereoscopic films. Experience with this combined technique has been recently published by Steele and Javert.

It has been appreciated for a long time that the addition of the isometric scale principle to the frontal film would simplify the measurement of the transverse diameters. The scale must occupy the same plane above the table as the diameter which is to be measured. The scale should be used independently of any direct external measurement of the patient, so that any x-ray technician can perform the procedure. Reading of the films would be simplified for those individuals lacking stereoscopic vision, or those unwilling to devote sufficient time to develop skill in using the stereoscope, as is the case with the microscope.

When using the Thoms' grid technique, it has always been questionable as to the placement of the grid in the proper plane for both the anteroposterior diameter and the transverse diameter of the inlet.

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The latter is invariably below the AP diameter (between the promontory and symphysis) as shown in Fig. 1. The relationship of these diameters measured on the grid, which is exposed at an angle to the film, frequently results in lengthening of the AP diameter and shortening of the transverse diameter. Very recently, Thoms has modified this technique



Fig. 1.—Showing that when the AP diameter of the inlet is drawn through the sacral promontory, the transverse diameter lies about 2 cm. below it. This results in unequal distortion on the x-ray film. Placing the true conjugate in the plane of the ileopectineal lines corrects this error somewhat (see Fig. 2).

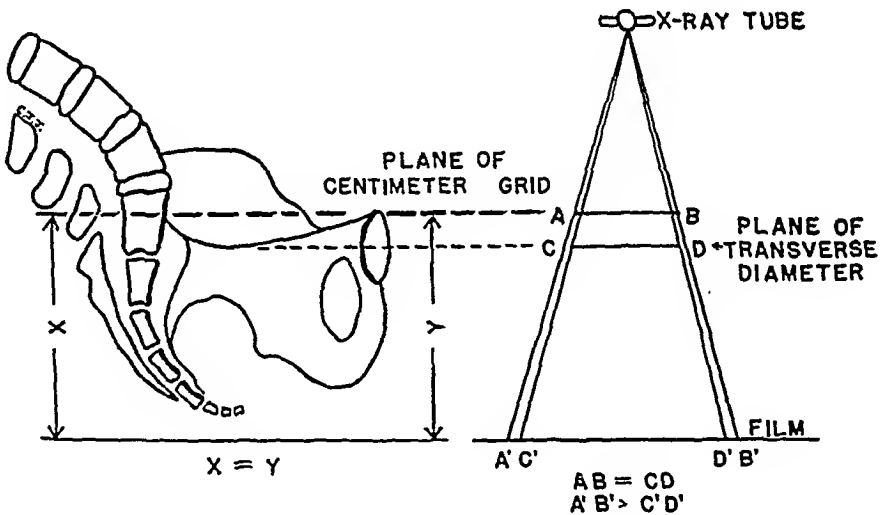


Fig. 2.—When the AP diameter of the inlet is drawn in the plane of the ileopectineal lines, the transverse diameter will often lie beneath it, therefore, positioning the patient so that X equals Y still results in unequal distortion but to a less extent than in Fig. 1.

by placing the scales parallel to the film as shown in Fig. 2. He has also included scales for measurement of various planes throughout the pelvis and utilizes the AP diameter in the planes of the ileopectineal lines as recommended by Caldwell and Moloy. He retains the use of external anatomic landmarks to ascertain the plane of the inlet as shown

in Fig. 2. In spite of these added precautions, the transverse diameter will still be found below the AP plane in certain patients.

To overcome these obstacles, a set of centimeter scales similar to those used by Rowden and Walton were exposed at horizontal levels ranging from 1 to 14 cm. above the x-ray table. The films were then mounted in a picture frame behind glass so that they could be placed before any ordinary view box as shown in Fig. 3. Transmitted light permits direct

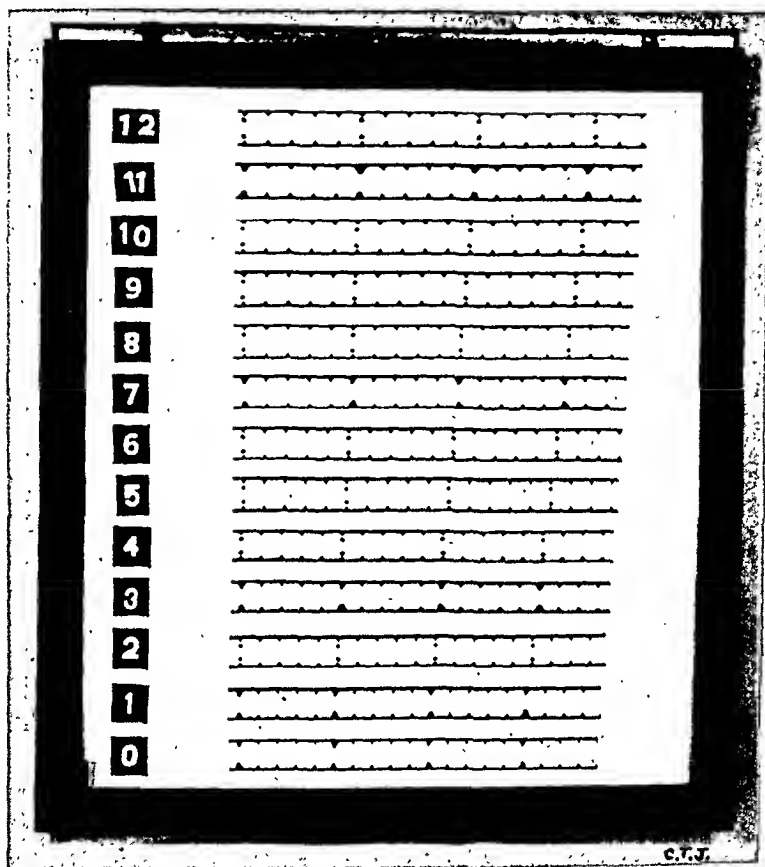


Fig. 3.—Distorted centimeter scales, in a picture frame, made by placing a rule at various levels ranging from 1 to 14 cm. above the x-ray table. Transverse diameters shown in Fig. 6 can be measured directly on these scales when placed before an ordinary view box, provided that the vertical levels of these diameters have been obtained from the lateral film.

measurement of any *transverse* diameter on the frontal film when held over the proper scale. Selection of the scale for the proper plane is determined directly from the lateral film and will be discussed below.

The *combined* isometric scale and stereoscopic techniques are comprehensive. Mensuration can be practiced by those unable to use the stereoscope and where such apparatus is not available. The latter instrument is retained in the technique in order to visualize cephalopelvic size relationship, pelvic architecture, position of the occiput, and the mechanism of labor including lever actions. Since the course and outcome of labor are the resultant of the mechanical forces (static and dy-

namie) involved in the process, this valuable aid for their evaluation should be employed when possible both in diagnosis and prognosis. Appreciation of its outstanding value for teaching purposes will assure its use for instruction of students. Any ordinary stereoscope can be used. The precision stereoscope is necessary for mensuration and serves as a check on those obtained from the isometric scales. The technique requires no special radiographic equipment, nor do the x-ray technicians require special training.

RADIOGRAPHIC TECHNIQUE

The Caldwell-Moloy technique is employed for the stereoscopic frontal films with several important exceptions. The patient lies in the recumbent position, as shown in Fig. 4, with the shoulders elevated by two pillows placed lengthwise and a 4-inch rolled pad is placed under the lumbosacral curvature. This position tilts the pelvis forward and is not the least uncomfortable. A more direct view of the inlet is obtained.

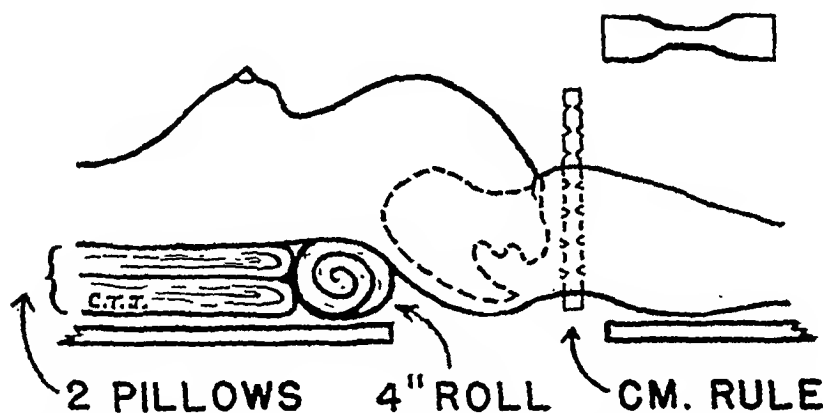


Fig. 4.—Positioning of the patient on the x-ray table for exposure of the frontal stereoscopic films, omitting the centimeter rule. Identical position is assumed for the lateral film on a board with the central portion cut away (see inset), and addition of the rule.

A wooden rod containing two leaden markers 9 cm. apart is placed under, instead of over, the patient. This insures a more constant position of the marker images in the direct line of vision. Setting of the stereoscope is facilitated and greater accuracy is assured. The tube is centered on the midpoint of an imaginary line connecting the anterior superior spines, 25 inches from the film. It is then shifted cephalad for $1\frac{1}{4}$ inches. A Bucky diaphragm is used and the film is exposed for about four to ten seconds. The tube is then shifted caudally for $2\frac{1}{2}$ inches ($1\frac{1}{4}$ inches from imaginary line) for exposure of the second film.

The patient is now removed to the stretcher on which has been placed a suitable board made of plywood and having the shape of a dumb-bell (see insert, Fig. 4). The hips are placed over the narrow mid-portion of the board so that reflection of the x-rays and undesirable images are minimized. The shoulders and legs rest on the wider portions of the board. Positioning of the patient is performed exactly as described above with the exception that a metal centimeter rule is now

placed in a vertical position in front of the symphysis, as shown in Fig. 4. This technique was devised by Javert and Steele in 1935 as a modification of that used by Granzow. Since it was not unlike that presented by Weitzner in the same year, it was never published. Thoms reported a similar procedure in 1937 with the patient in a vertical position and the scale behind her.

The x-ray table is raised to a vertical position and the stretcher is placed before the film with one hip touching the x-ray table and held in position with a binder. The tube is centered on an imaginary line between the trochanter and the posterior superior spine, at a distance of 36 inches. The exposure varies from twelve to 20 seconds, depending on the thickness of the patient. The distance may be increased to 50 inches in a thin patient, provided that the generator is sufficiently powerful. The exposure varies from eight to twenty seconds, depending on circumstances.

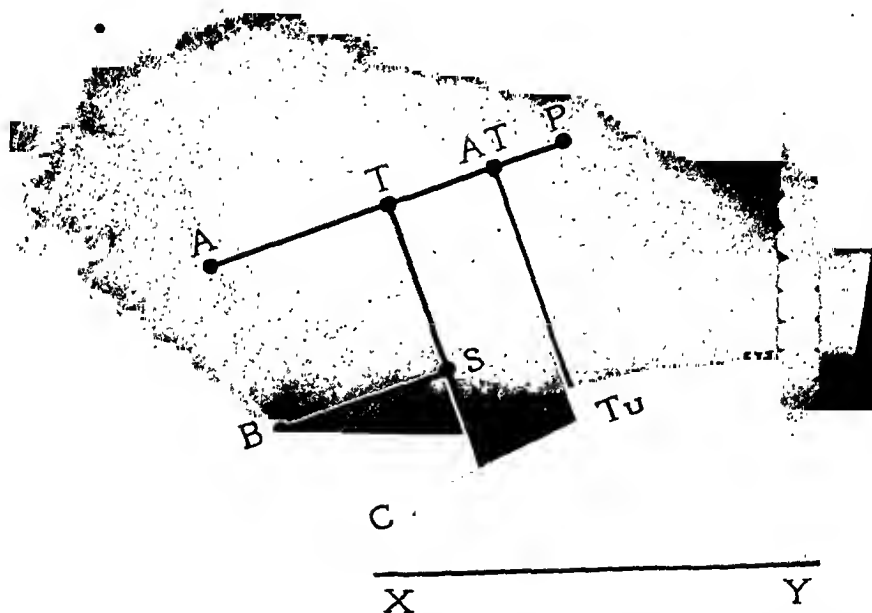


Fig. 5.—Lateral film. X-Y is drawn through the lower tip of the ruler parallel to the shadow of the board, and perpendicular to the ruler. The anteroposterior diameter (A-P) is drawn in the plane of the ileopectineal lines projected on the sacrum and symphysis. B-S is drawn parallel to A-P. C-Tu is the posterior sagittal diameter of the outlet. Points T, AT, S, and Tu mark the vertical planes of their respective transverse diameters from baseline X-Y.

A 45-degree angle film is also taken as originally recommended by Caldwell and recently recommended by Thoms.

Four films are required. Those desiring to use the technique without the stereoscope need take only two films, the lateral and one frontal film.

ANALYSIS OF THE LATERAL FILM, MEASUREMENT OF AP DIAMETERS

Certain lines, shown in Fig. 5, are drawn on the lateral film placed in a view box, using a red wax pencil. Line A-P denotes the obstetric conjugate of the inlet. It lies in the plane of the ileopectineal lines, and is drawn from a projection of these lines on the posterior surface

of the pubis and the anterior surface of the sacrum. Line $B-S$ is drawn parallel to $A-P$ and passes through the bases of the ischial spines. Line $C-Tu$ passes from the tip of the sacrum to the tuberosities. Vertical line $T-S$ transects the base of the ischial spines, and $AT-Tu$ bisects the are formed by the ischial tuberosities.

A baseline, $X-Y$, is drawn from the lower tip of the centimeter rule parallel to the image of the board which was placed under the patient at the time of exposure. If the image of the board is not visible, $X-Y$ can be drawn perpendicularly to the centimeter rule. Therefore, the vertical heights of points T , AT , S , and Tu can be readily obtained. They represent the planes of the transverse, anterior transverse, interspinous, and intertuberosus diameters, and are recorded in centimeters.

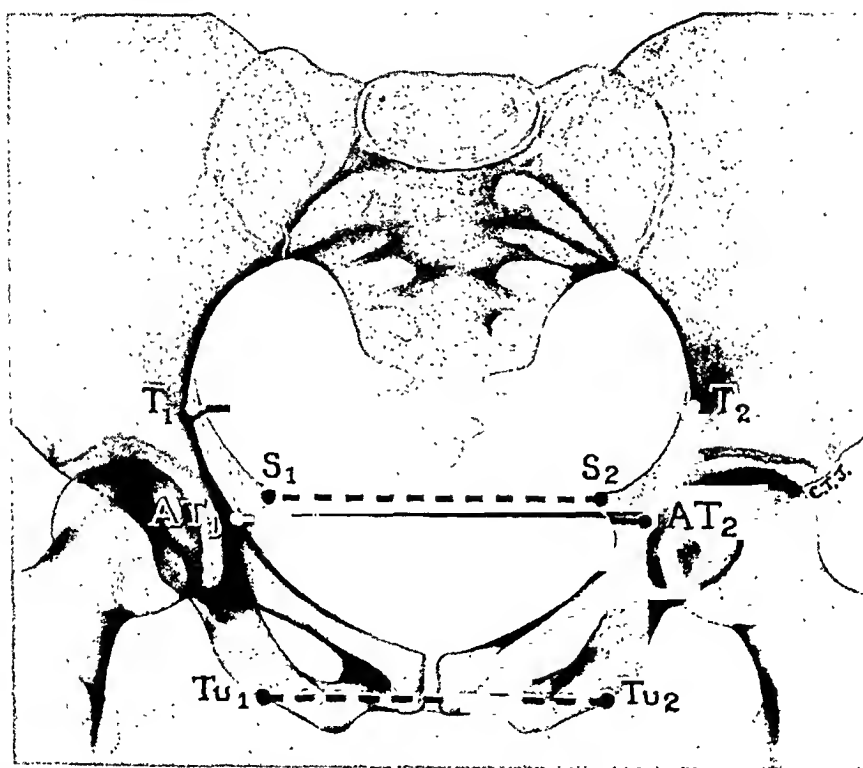


Fig. 6.—Frontal film. Showing the transverse (T_1-T_2) and anterior transverse (AT_1-AT_2) diameters of the inlet; and the interspinous (S_1-S_2) and intertuberosus (Tu_1-Tu_2) diameters which can be measured on the scales shown in Fig. 3, provided that the proper scales are employed for the same planes.

Only anteroposterior diameters are measured in the lateral film. Calipers are used. The distance between $A-P$ is measured directly on the isometric scale, as can the posterior sagittal diameter of the inlet, $A-T$, and the diameters of the midpelvis and the outlet. The vertical depth of the pelvis can be measured at any point.

ANALYSIS OF THE FRONTAL FILMS, MEASUREMENT OF TRANSVERSE DIAMETERS

The widest diameter of the inlet is designated by line T_1-T_2 in Fig. 6. The anterior transverse diameter is designated by line AT_1-AT_2 , which is drawn between the ileopectineal eminences situated at the thinnest

portion of the acetabula. Lines S_1-S_2 and Tu_1-Tu_2 represent the interspinous and intertuberal diameters, respectively. The planes of these diameters can be located readily from the lateral film as shown in Fig. 5. The transverse diameters can be measured with calipers or by placing

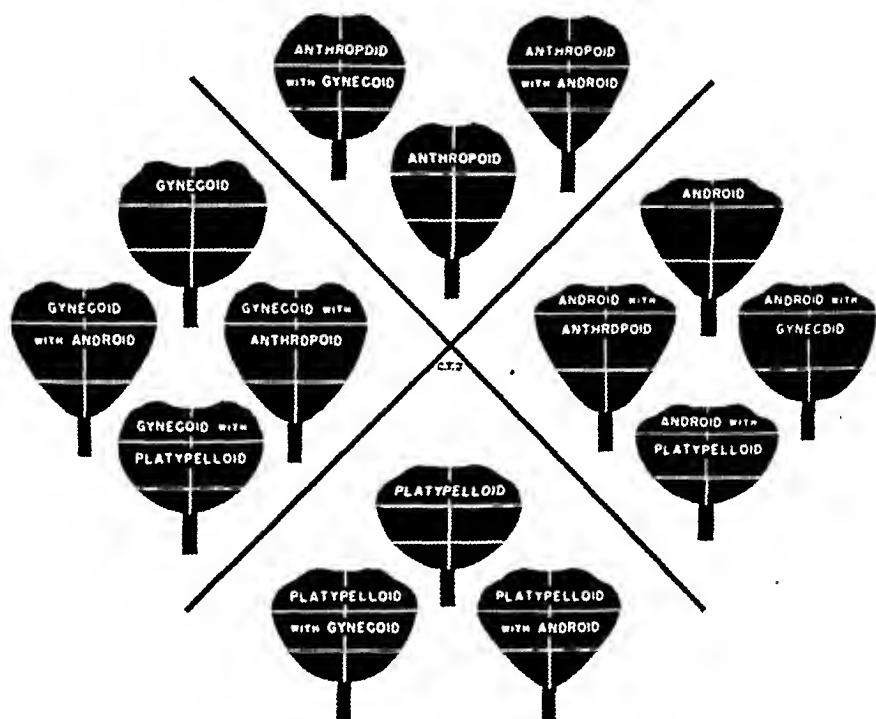


Fig. 7.—Theoretical models of the inlet based on the parent pelvic types shown in Fig. 9 assist in pelvic classification on the basis of morphology.

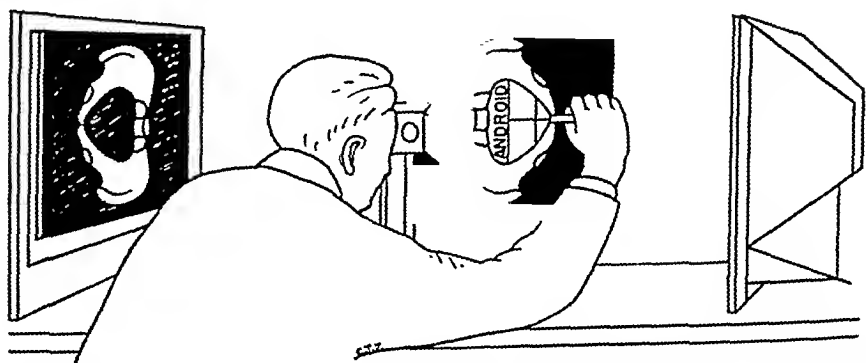


Fig. 8.—Use of the ordinary stereoscope for classification of the pelvis using models of the inlet shown in Fig. 7. A precision stereoscope must be employed for mensuration.

the film directly over the set of distorted scales shown in Fig. 3, in front of a view box. Each diameter is measured on the scale corresponding to the vertical height of the plane in which it lies.

STEREOSCOPIC STUDY

The two frontal films are placed in the stereoscope. Pelvic architecture of the brim, the canal, and the outlet can readily be studied. The

use of models of the inlet shown in Fig. 7 assists in classifying the pelvis as indicated in Fig. 8. Cephalopelvic size relationships are readily noted. If the precision stereoscope described by Moloy is available, mensuration of the anteroposterior, the anterior transverse and transverse diameters of the inlet can be carried out. The interspinous diameter can be measured as well as the intertuberal. Diameters of the fetal head can also be measured except in a few instances where extremely oblique images occur. Measurements in the stereoscope serve as a valuable check on those obtained from the isometric scales and vice versa. Preliminary marking of the films as shown in Fig. 6 makes measurement easy even to the novice.

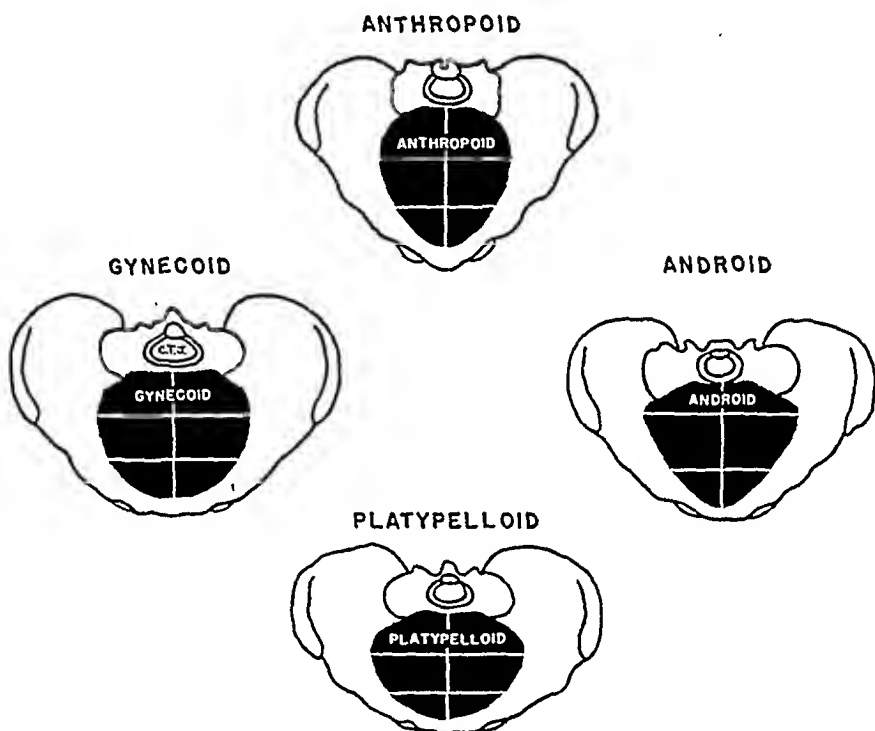


Fig. 9.—The four-parent pelvic types (after Caldwell and Moloy), based on morphology of the inlet. The anterior transverse diameter drawn between the ileopectineal eminences, the transverse diameter, and the AP and posterior sagittal diameters from the lateral film, assist in pelvic classification on the basis of mensuration.

The view of the inlet is more direct than that obtained with the original Caldwell-Moloy technique so that pelvic architecture is more readily apparent and measurements can be made with greater ease and accuracy. Position of the head, its obliquity, and the degree of flexion can also be ascertained.

THE ANTERIOR TRANSVERSE DIAMETER OF THE SUPERIOR STRAIT

This important diameter, hitherto undescribed in the available obstetric or anatomic textbooks, provides an important additional diameter of great value in classification of the pelvis. It is drawn between the ileopectineal eminences which are represented by the thinnest portions of the acetabula as the ileopectineal line is approached on either side

of the frontal film as shown in Fig. 6. This diameter provides the key to the type of forepelvis, readily perceiving the android type of pelvis, and assists in classification of the pelvis. Thoms has classified pelves using only the AP and transverse diameters, exposed with unequal distortion. These diameters, together with the anterior transverse diameter, and the posterior sagittal diameter of the inlet, may be used when mensuration is the basis for classification. Models of the inlet, shown in Fig. 7, are also useful. A common ground has been reached for the classification of pelves on a basis of mensuration and morphology as shown in Fig. 9. This subject will be discussed more fully in a subsequent communication.

CEPHALOMETRY

Measurement of the biparietal, occipitofrontal and suboccipitobregmatic diameters of the fetal head can be carried out with the precision stereoscope in the majority of the cases. However, when the head lies in either marked Litzmann's or Naegele's obliquity, difficulty in accurate measurement is sometimes encountered. Therefore, estimation of cephalopelvic relationship in terms of fetal-maternal diameters per se may sometimes lead to erroneous deduction. It is believed such estimation should be performed visually in the stereoscope and dependence on actual measurement relegated to secondary importance. The fetal bony skeleton (including the head) develops only slightly in the last month of gestation, whereas, the tissues do increase in weight. Estimation of the weight of the infant from the diameters of the head in the x-ray is not practiced routinely for the above reasons.

PELVIMETRIC STATISTICS

The results of mensuration of four dried pelves, using the isometric scales principle in lateral and frontal films and the parallax principle of the stereoscope, are shown in Tables I and II. As can be seen, the average error is 0.5 mm. or less. A number of patients have been examined to date with satisfactory results with the *combined* technique described above.

TABLE I. COMPARISON OF ANTEROPOSTERIOR DIAMETERS IN DRIED PELVES AND IN LATERAL FILMS

DIAMETERS (SEE FIG. 5)	AP	AT	BS	C-Tu
<i>Pelvis A:</i>				
Dried pelvis	11.6	5.6	5.3	5.8
Lateral film	11.2	6.0	5.2	6.1
Stereoscope	11.1			
<i>Pelvis B:</i>				
Dried pelvis	11.0	4.8	5.3	5.0
Lateral film	10.8	5.2	5.1	5.1
Stereoscope	10.8			
<i>Pelvis C:</i>				
Dried pelvis	10.7	5.5	5.8	8.0
Lateral film	10.6	4.5	6.2	8.3
Stereoscope	10.8			
<i>Pelvis D:</i>				
Dried pelvis	10.6	4.4	5.6	8.0
Lateral film	10.5	5.0	5.2	7.5
Stereoscope	10.7			

TABLE II. COMPARISON OF TRANSVERSE DIAMETERS IN DRIED PELVES AND IN FRONTAL FILMS

DIAMETERS (SEE FIG. 6.)	T_1-T_2	AT_1-AT_2	S_1-S_2	Tu_1-Tu_2
<i>Pelvis A:</i>				
Dried pelvis	13.8	11.8	11.4	12.0
Frontal film	13.4	11.8	11.0	11.9
Stereoscope	13.5	11.6	11.8	12.1
<i>Pelvis B:</i>				
Dried pelvis	12.9	12.4	12.5	13.3
Frontal film	12.7	12.25	11.9	13.0
Stereoscope	13.4	12.2	12.4	13.2
<i>Pelvis C:</i>				
Dried pelvis	13.2	11.5	10.9	12.2
Frontal film	13.2	11.0	10.6	12.5
Stereoscope	13.3	11.7	11.3	12.3
<i>Pelvis D:</i>				
Dried pelvis	13.7	12.0	11.1	12.5
Frontal film	13.3	12.0	11.25	12.7
Stereoscope	13.4	12.2	11.0	12.3

SUMMARY

1. A combined isometric and stereoscopic technique provides for adequate roentgenographic survey of the obstetric pelvis. Both the lateral and frontal films are taken under identical positioning of the patient.

2. A lateral film containing an isometric scale is employed for measurement of the anteroposterior diameters of the pelvic canal and for the vertical heights of the various planes of the transverse diameters.

3. A distorted set of scales has been developed for measuring the transverse diameters of the pelvis directly on the frontal film. The planes to be used are obtained directly from the lateral film.

4. Only two films are essential. However, for complete examination, another frontal stereoscopic film, and a 45-degree angle film of the pubic arch are recommended. The national emergency may warrant dispensing with the extra films and the stereoscope.

5. Nevertheless, the precision stereoscope is preferred when available, for study of pelvic architecture and cephalopelvic relationship and labor mechanisms, as well as a check on measurements obtained from distorted images with the isometric scales.

6. Workup of the lateral and frontal films together eliminates the location of uncertain external anatomic landmarks, and measurements on the patient.

7. Introduction of an anterior transverse diameter of the inlet, drawn between the ileopectineal eminences, should assist in detecting variations in the forepelvis.

8. Mensuration of the AP diameter, the transverse, the anterior transverse, and the posterior sagittal diameter of the inlet provides a basis for classification of pelvis.

9. A common ground has been reached for pelvic classification on the basis of mensuration and morphology.

10. Cephalometry can be performed. Estimation of the weight of the infant from the size of the head is no longer practiced.

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X-RAY LOCALIZATION OF THE PLACENTA*

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PAINLESS bleeding in the last trimester of pregnancy is a constantly recurring problem. The critically ill patient, bled out and in shock, is more often a problem in treatment than in diagnosis. Patients with small single or repeated episodes of painless bleeding, suspected of having placenta previa, are often subjected to rectal or vaginal examination, with the danger of sudden massive hemorrhage. To avoid this difficulty, among others, several investigators, in the last ten years, have introduced roentgenographic methods for the localization of the placenta, with special reference to the precise diagnosis of a previa.

Amniography, introduced by Menees, Miller and Holly¹ in 1930, and modified by Kerr and MacKay,² and by Burke,³ has never been very widely employed because of its dangers. Intravenous thorotrast, suggested by Ehrhardt⁴ in 1932, similarly was quickly abandoned. In 1934 Snow and Powell⁵ described a method of direct visualization of the placenta without preparation. Employing a soft tissue technique, they localized the placenta in the fundus in 60 routine cases, but at that time

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had no cases of placenta previa. Later the same year Ude, Weum, and Urner⁶ reported on a cystographic method for detecting widening of the normal soft tissue space between the bladder and the fetal skull. They used 12.5 per cent sodium iodide in the bladder as a contrast medium. Symmetrical widening of the space was used as the criterion for the diagnosis of central placenta previa, and unilateral widening for the diagnosis of partial placenta previa.

In 1935 Ude and Urner⁷ reported on 35 cases of last trimester bleeding, with 14 accurately diagnosed as placenta previa. It was at first thought that breech and transverse presentations precluded the possibility of accurate diagnosis by this method, but subsequent work has shown that if any part of the fetus is resting against the concave surface of the placenta, diagnosis is possible.⁸

There are conflicting opinions concerning the value of the cystographic method. A number of observers have achieved satisfactory results, but its reliability is questioned by Holmes,⁹ Carvalho,¹⁰ Arnell and Guerriero,¹¹ and by Hundley and his co-workers.¹² Others^{13, 14} consider it of limited value, with greater accuracy in ruling out placenta previa than in diagnosing it. Some of these differences appear to be due to technical difficulties, errors in interpretation, or to variations in the criteria for distinguishing normal from abnormal.

Several modifications of technique have been introduced in an attempt to improve the accuracy of the method. McDowell¹⁵ has suggested repetition of the films after withdrawal of some of the contrast medium should the fetal head be obscured. A 5 per cent solution of sodium iodide was used by Friedman and MacDonald¹⁶ and by Wells.¹⁷ Prentiss and Tueker,¹⁸ and Snow and Rosensohn¹⁹ have employed air in the bladder instead of an opaque medium, with good results.

Placentas situated on the posterior wall of the lower uterine segment have been difficult to detect, since their bulk is not interposed between the bladder and the head of the fetus. Oblique and lateral cystogram films have been of some assistance. Snow and Rosensohn¹⁹ have used air in the rectum to show these placentas more clearly.

Relatively few investigators have routinely employed the lateral soft tissue roentgenograms introduced by Snow and his co-workers. Ude, Urner, and Robbins⁸ have admitted their value in certain types of cases. Brown and Dippel,²⁰ by combining aerocystograms with soft tissue roentgenograms, have attained a very high degree of accuracy, though in 17 per cent of 53 bleeding cases the diagnosis could not be made, either positively or negatively.

In this paper we wish to report our experience with certain of these methods. The clinical material consists of 126 cases of painless bleeding in the last trimester of pregnancy, studied during the past four years. Most of these were clinic patients, except for 14 emergencies and 15 private patients.

Our methods and routine of examination have undergone modification since we started this work in 1936, but at present consists of two separate procedures. Routinely, during the past sixteen months, we have first

taken right and left laterals of the entire uterus with a technique which is designed to give maximum soft tissue contrast, as described by Snow and Powell.

These films are taken with the patient recumbent, lying comfortably on her side. No special apparatus is necessary. The factors employed vary with the equipment at hand, but low voltage and relatively high speed are essential. We use 60 Ma with a target-film distance of 36 inches. The KVP varies between 65 and 70 and the time between three and four seconds, depending upon the obesity of the patient. Ultra-speed film is used with a high speed double intensifying screen, and a

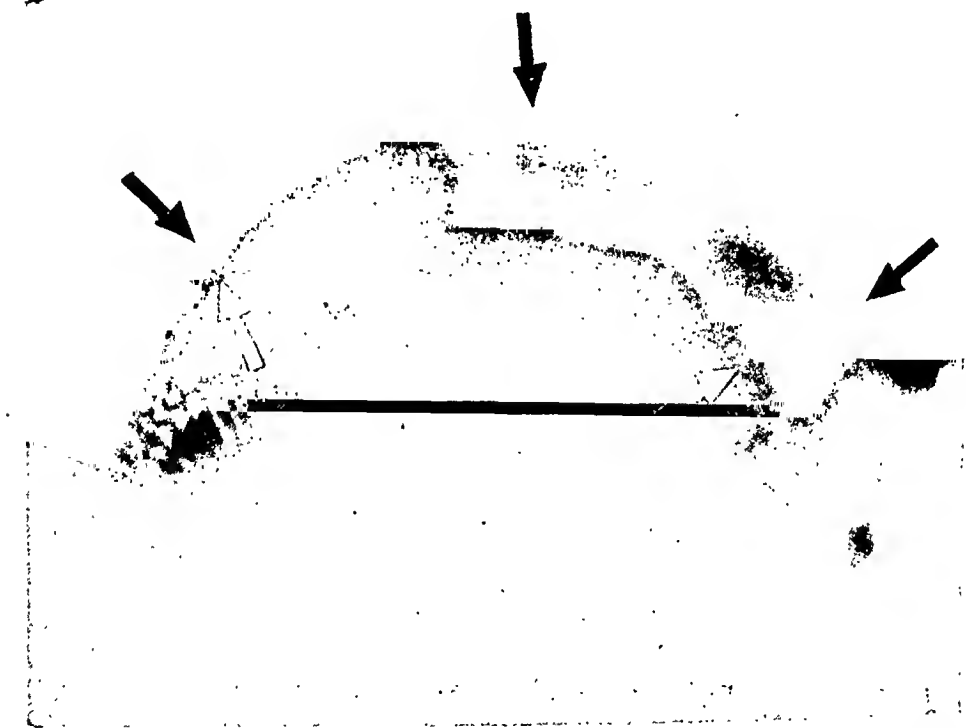


Fig. 1.—Lateral soft tissue roentgenogram. Arrows indicate placenta normally situated on anterior uterine wall. Vertex presentation. Note line of demarcation caused by subcutaneous fat of fetus.

Potter-Bucky diaphragm. Films are developed by sight, without accurate time or temperature control. Most are viewed in an ordinary light box, but some require a concentrated source of light, as from an uncovered incandescent bulb, to bring out detail. Facility in interpretation is acquired only after study and experience.

The placenta is visualized in the lateral film as a fusiform thickening on the wall of the uterus, reaching an average thickness of 7 cm. at its midportion. It occupies from one-third to one-fourth of the uterine wall, and in the great majority of instances is located in the upper half of the uterus on the anterior or posterior surface. When, however, the mass of the placenta is seen below the equator of the uterus, the lower

edge often extends into the lower uterine segment, to encroach upon or cover the internal os. Almost invariably the fetal small parts face the placenta, at times causing visible indentations. A black line of demarcation, shown by Snow and Weintraub²¹ to be due to increased radio-translucency of the subcutaneous fat of the fetus, is sometimes helpful in locating the placenta.

By this soft tissue technique we have been able to localize the placenta in 86.1 per cent of the 108 cases where this procedure was employed. Of these, 74 were fundal, on the anterior or posterior wall,

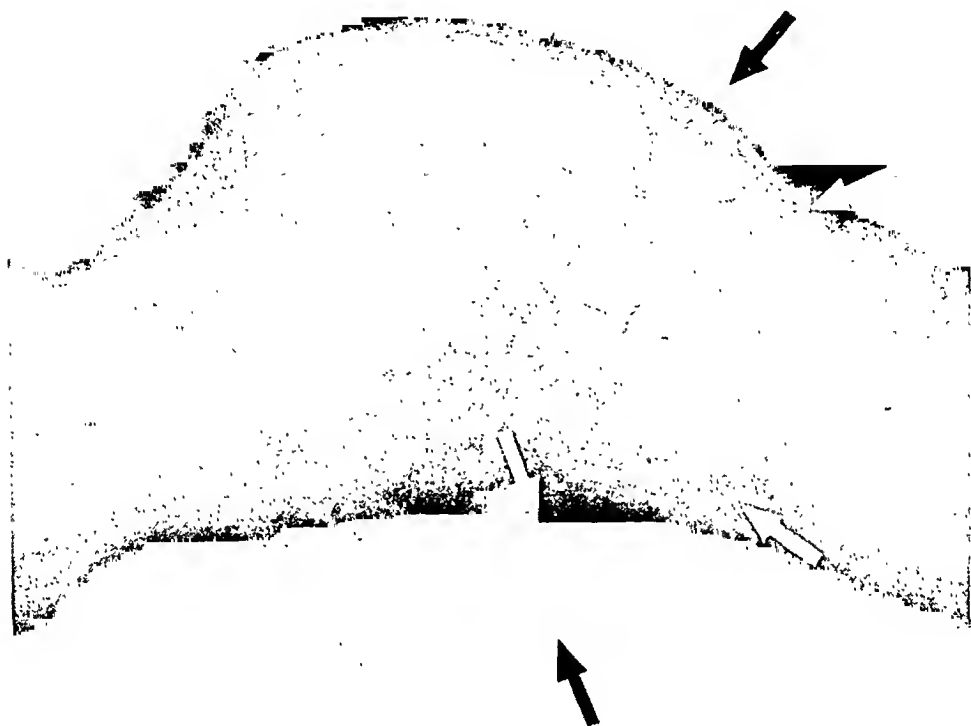


Fig. 2.—Normal lateral soft tissue film showing placenta located high on posterior wall of uterus. Vertex presentation.

and 19 showed the placenta to lie wholly or in part in the lower uterine segment. In 9 no placenta was seen and in 4 there was uncertainty about the significance of the shadows.

In 7 of the 9 cases where no placenta was visualized, placenta previa was subsequently demonstrated by our second method of examination. Hence, we consider that absence of the placental shadow strongly but not invariably suggests placenta previa. In the 19 cases where the placenta was visualized low in the uterus, diagnosis of the presence or absence of placenta previa was feasible in only 6. Placenta previa was subsequently shown to be present in 7, a low implantation in 5, and in 7 others no definite placental pathology was finally demonstrable. We

have not, therefore, in most instances, tried to make an absolute diagnosis of the presence or type of placenta previa from the soft tissue films alone, but selected these cases for further x-ray study.

In 2 cases of placenta previa false negative diagnoses were made on the soft tissue films. One showed a normal implantation, yet a marginal placenta previa was found on cystogram. In the second a misleading diagnosis of fundal implantation was made. Subsequent vaginal examination revealed partial placenta previa, confirmed at operation.



Fig. 3.—Normal cystogram with arrows pointing to symmetrical soft tissue space between fetal skull and bladder filled with sodium iodide. No increase in width. No placenta previa.

However, the bulk of the placenta was actually fundal in location and only a long, thin tongue of placenta extended down to the internal os. This unusual type of placenta must be kept in mind, as well as succenturiate and partite placentas. Accurate localization by this method may be interfered with by prematurity or obesity. Difficulty from abnormal presentations, multiple pregnancy, and hydramnios has been reported.

Our second method of examination is now employed only in those selected cases where soft tissue x-rays either fail to reveal the placenta, show it to lie partly in the lower uterine segment, or are equivocal.

We modified the original cystographic method soon after starting its use in 1936. At present it consists of anteroposterior x-rays of the pelvis taken by a precision stereoscopic technique with 4 per cent sodium iodide in the bladder. In these films also a modified soft tissue technique is employed.

The purpose of these films is to demonstrate an increase in the thickness of the soft tissue space lying between the presenting part and the filled bladder. Normally this space is occupied by the bladder wall, the peritoneal reflections between the bladder and uterus, the lower uterine segment, the membranes, and the fetal scalp. It measures from 1 to

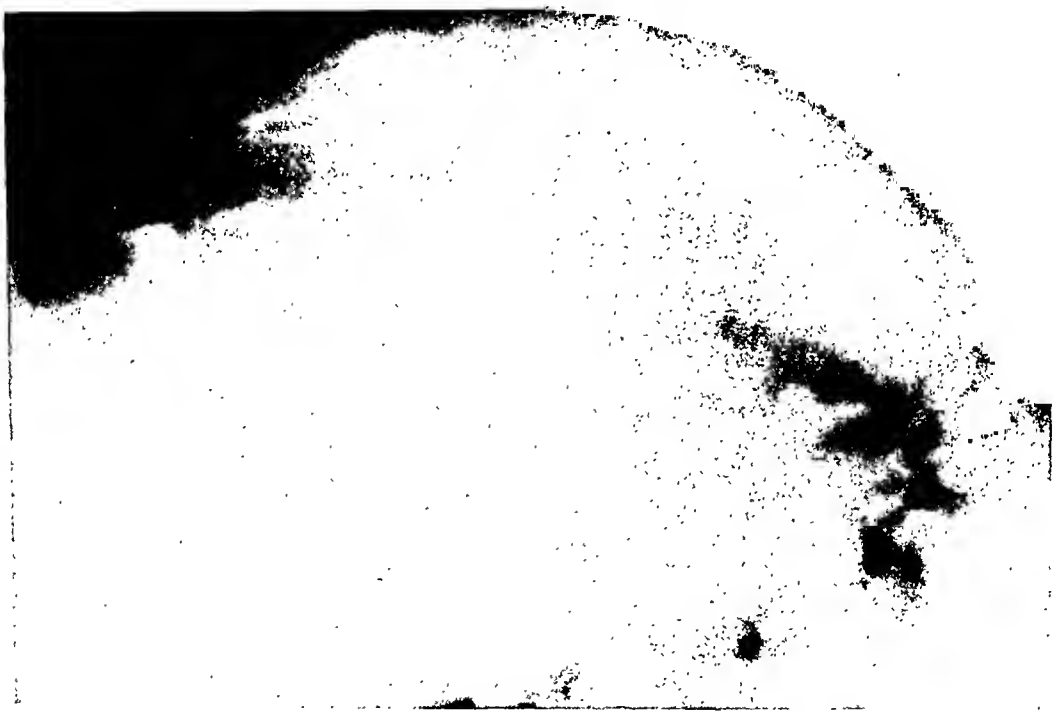


Fig. 4.—Primipara with painless bleeding at eight months. Placental shadow completely absent from fundus.

2 cm. in thickness. In central placenta previa the interposition of the placental mass may increase the distance to 5 or 6 cm. With marginal or partial previas, there is unilateral widening, either anteriorly, posteriorly, or laterally.

In several details our method of making cystograms varies from those described by others. We observed that the 25 to 40 c.c. of sodium iodide generally advocated, through filling the bladder only partially, led to false positives in cases where the head was unengaged, the fetus premature, or the presentation abnormal. By increasing the amount of sodium iodide in the average case to 125 c.c., and in some even up to 200 without discomfort, we have been able to fill the soft tissue space and

mold the bladder closely against the presenting part. The occasional resultant overlapping of the bladder and skull shadows has been overcome by using only 4 per cent sodium iodide instead of the usual 12.5 per cent. This not only does away with bladder irritation, but produces a translucent shadow, through which the fetal skull can readily be seen. It also produces a double bladder shadow, throwing the anterior and posterior horns into relief. When these stereoscopic films are viewed in the precision stereoscope, widening of the soft tissue space and deflection or distortion of the anterior or posterior horn of the bladder



Fig. 5.—(Same case as Fig. 4.) Cystogram showing marked widening of soft tissue space. Central placenta previa confirmed at operation.

can very accurately be determined. One need not depend solely on precise measurement of the soft tissue space to determine the presence of widening. At times the placenta itself is seen. This technique facilitates diagnosis where there is a breech or transverse presentation.

Our routine in handling last trimester bleeding cases now includes hospital admission, immediate blood typing, and cross-matching. No enemas or colonic flushes are given, nor is the patient examined rectally or vaginally. Soft tissue films are obtained and if indicated, cystograms

are made. In some cases, both methods are employed at once. If placenta previa is definitely diagnosed, no vaginal examination is made. If the placenta is fundal in location, or if it is not possible by x-ray to differentiate marginal placenta previa from a low implantation, a sterile vaginal and speculum examination is carried out, to determine the exact source of the bleeding. Facilities are at hand for treating any emergency situation that might arise.

By coordinating these two methods we have been able to localize the placenta in 97.6 per cent of our cases. We have had 17 cases of placenta previa and the diagnosis was accurately made in 16. In the

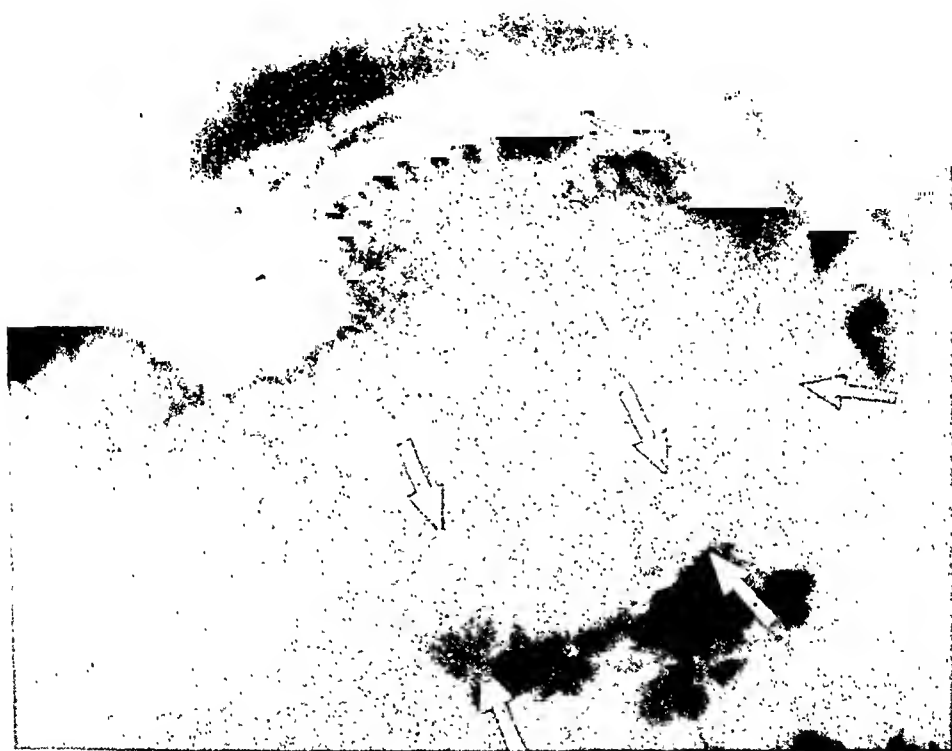


Fig. 6.—Secundipara with two episodes of painless bleeding in eighth month. Placenta low on posterior wall extending into lower uterine segment.

seventeenth case, already noted, a false negative diagnosis was made. While the degree to which the placenta covers the os has been accurately determined in most cases, in a few it has been greater than diagnosed.

It is obviously not intended that these x-ray procedures entirely supplant vaginal examinations in suspicious bleeding cases. However, the risk of starting a serious hemorrhage in an undiagnosed case of placenta previa is very great and even in a hospital such a hemorrhage may be rapidly fatal. By detecting these cases roentgenographically, we have reduced such examinations considerably. In our 17 cases of placenta

previa only 6 were examined vaginally and 3 of these for induction purposes. In the other bleeding cases, we felt safe in proceeding with a vaginal examination. No hemorrhages were produced in the entire series, and there were no induced premature labors or infections.

These x-ray methods have brought a feeling of security into the handling of bleeding cases. Instead of waiting indefinitely for the bleeding to stop, followed by a risky vaginal examination, diagnosis has now

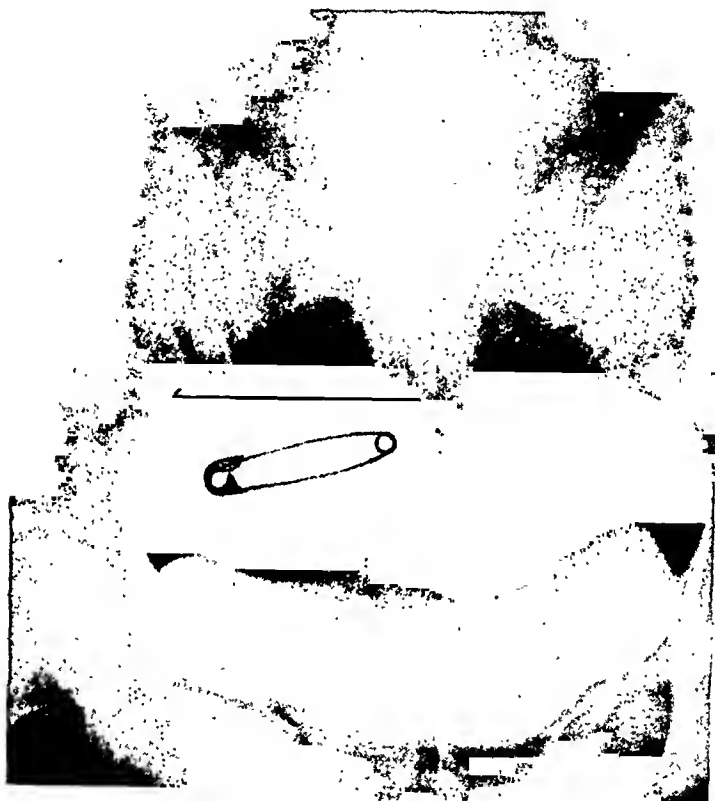


Fig. 7.—(Same case as Fig. 6.) Cystogram showing marked asymmetrical widening of soft tissue space due to intervening placenta. Marginal placenta previa at operation.

become prompt and much more certain, leading to earlier and safer treatment. The number of hospital days has been very greatly reduced. Patients can now be sent home for the remainder of their pregnancy with the physician secure in the knowledge that, should bleeding recur, no placenta previa is present.

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OBSERVATIONS ON HEMOLYTIC STREPTOCOCCUS INFECTIONS FOLLOWING DELIVERY AND ABORTION SINCE THE ADVENT OF SULFANILAMIDE*

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PUERPERAL and postabortal infections have maintained a conspicuous position among the dangerous complications of pregnancy from the earliest of medical records until the present time. While the majority of such infections showed a strong tendency to spontaneous recovery, a group caused by the hemolytic streptococcus constituted a special problem, because of its tendency to be associated with epidemic outbreaks of a very serious nature, associated with a high mortality, and because of the frequency of fatal outcome in many of the endemic cases. This report is concerned only with this variety of infection.

Because this severe and often fatal type of infection has come under the control of specific agents, it is wise at this point to recall briefly the picture presented before the advent of modern chemotherapy. Clinically it was possible to divide such infections into three main types: First, patients with little or no febrile reaction, in whom the disease appeared to be localized to the genital tract. Serologic investigation of the hemolytic streptococci recovered from such cases often showed the organisms to belong to other groups than A. Second, patients in whom the infection was associated with severe febrile reaction but with no immediate evidence of extension to the blood stream or peritoneum. Delayed septicemia occurred in a certain proportion of such cases. Third, patients who showed an immediate extension of the infection to

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Much of the bacteriologic and serologic work was carried out under a grant from the Commonwealth Fund.

the blood stream or peritoneum from the uterus associated with a severe febrile reaction. This group was aptly called fulminating streptococcus sepsis. In these last two types the causative hemolytic streptococcus has been found serologically to belong to Group A in the vast majority of instances.¹ Infections of the first type were problems from an epidemiologic viewpoint, while the second and, particularly, the third presented the most serious outlook to the individual.

Patients classified in the second group frequently ran a prolonged course of severe illness, marked by fever and the appearance of pelvic parametritis. If septicemia or peritonitis did not appear, as a late manifestation, recovery eventually occurred through the development of natural immune mechanisms in the patient. Surgical intervention in the face of such infections, when localized, often resulted in the widespread dissemination of the organisms. As an example, the following case may be quoted:

A. F., aged 20 years, single, was admitted to Bellevue Hospital on Feb. 6, 1935, in the eighth week of pregnancy, complaining of fever and pain. She admitted introducing a foreign body into the cervix about two weeks previous to admission. Little bleeding followed this procedure until February 5 when she began to pass clots. On admission her temperature was found to be 101° F., and pulse 110. Abdominal examination was negative. Pelvic examination showed moderate bleeding from the cervix, which was soft and partially dilated. The uterus was about the size of a two months' pregnancy, freely movable, and slightly tender. The parametrium and adnexa were normal. A cervical culture was taken. These findings having been corroborated, a curettage was performed on the following day with the evacuation of a large amount of placental tissue. The cervical culture, unfortunately not reported until after the operation, showed a pure culture of hemolytic streptococcus. Following this procedure her fever rose to 104° F., and during the night she began to have severe abdominal pain. Marked diffuse tenderness and rigidity of the entire abdomen developed the next day. She complained of pain in the right chest, and auscultation revealed an area of fibrinous pleurisy. These symptoms gradually disappeared, the temperature falling to normal on the twenty-fifth postoperative day. Pelvic examination during this period showed a right parametritis. Repeated cervical cultures were positive for hemolytic streptococcus until shortly before discharge. Two days after her operation, her serum was found to contain large amounts of antifibrinolytic substance.² As a complicating feature this patient had rheumatic heart disease with mitral stenosis. She was discharged on the thirty-eighth day with a residual parametritis, and has remained well, having paid several visits to the follow-up clinic.

This summarizes a case in which the hemolytic streptococcus was the infecting organism, in all likelihood having been introduced during the attempt to produce abortion. This localized infection had resulted in the production of a defense mechanism, as evidenced, in part, by the production of antifibrinolytic substance in her serum. Nevertheless, curet-

tage apparently resulted in widespread dissemination of the organisms, which, however, were localized and disposed of upon their arrival in other tissues. The peritoneal, pleural, and parametrial reactions bear witness to this, as well as the failure to demonstrate septicemia. This patient was doubly fortunate in that she, a subject of rheumatic heart disease, was vulnerable to the establishment of bacterial endocarditis.

Rapidly spreading infections characterized by early septicemia or peritonitis, or both, can be more briefly summarized. After searching the records of the obstetric and gynecologic service at Bellevue Hospital from Jan. 1, 1933, to June 1, 1936, twelve such cases with septicemia were found. Ten of these resulted fatally, a mortality of $83\frac{1}{3}$ per cent. Only two recovered after a prolonged course of severe illness.

Treatment during this period was purely palliative and consisted in absolute bed rest, an adequate supply of fluids and food, and repeated transfusions. Surgical procedures in the presence of such an infection were contraindicated except for the drainage of localized abscesses.

The report by Colebrook and his associates³ in June, 1936, on the use of sulfanilamide in patients suffering from this type of infection aroused immediate interest throughout the world. Having secured an ample supply of the drug, a careful search was made at Bellevue Hospital for patients suffering from severe hemolytic streptococcus infections following abortion or delivery; none were encountered until the winter of 1938, and since then a few cases have been observed each year, the majority in 1940. Only one such patient has been found on the obstetric wards. She died after a prolonged post-partum septic course, showing a blood culture positive for the hemolytic streptococcus as a terminal event. Repeated efforts, during the course of her illness, failed to demonstrate this organism in the genital tract. She failed to respond to chemotherapy. Since this case does not fall into the general pattern and is not clearly understood, it will not be included among those to be reported. Aside from this case about ten mild infections by the hemolytic streptococcus have been observed on the obstetric service. All have been isolated and some treated with sulfanilamide. When so treated, the organisms disappeared rapidly from the genital tract. During this period, preventive methods have been in force, aimed principally at a reduction of such infections. It could be said that their low incidence on the obstetric service was entirely the result of such preventive methods, but knowing the rarity of such infections throughout the past five years, this statement would not be justified.

The thirteen severe localized or spreading hemolytic streptococcus infections to be reported have all been observed on the gynecologic service since 1938. While only a small group, it has been considered worth describing because this type of infection has been seen but rarely in New York City during the past five years. The number of cases

does not lend itself to statistical analysis. The histories will be briefly summarized in chronologic order, since during this period the method of treatment underwent gradual evolution. Each case is illustrated by a chart showing the temperature, cultural results, the daily and total dosage of sulfanilamide, and the additional forms of therapy used. The frequency with which the drug was administered will be noted in the summaries.

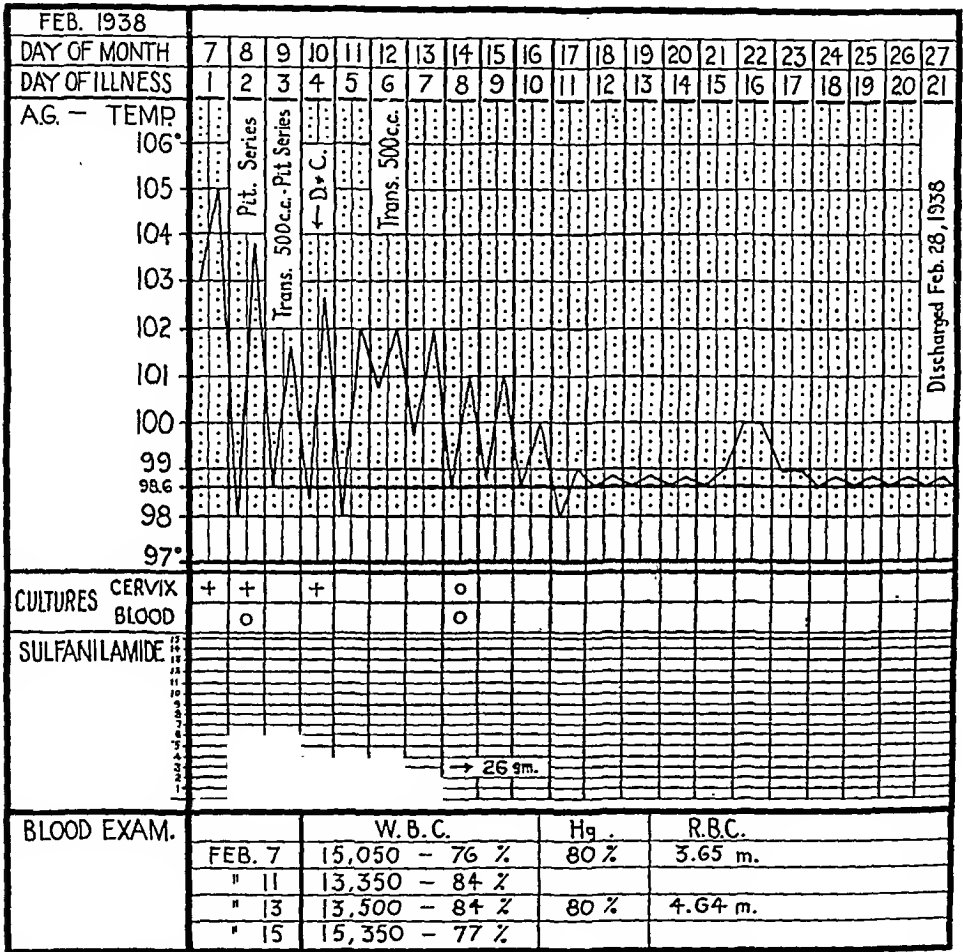


Fig. 1.—Case 1.

CASE 1.—A. G., a 34-year-old, married, white woman, gravida vii, para ii, was admitted on Feb. 7, 1938, in the third month of pregnancy, complaining of lower abdominal pain, backache, chills, and fever of two days' duration, and of vaginal bleeding for twenty-four hours. She denied attempts to induce abortion in the present instance, admitting successful efforts in three of her previous pregnancies.

Examination showed her uterus to be enlarged to the size of a three months' pregnancy, the cervix being soft, closed, with a bloody discharge. A cervical culture was reported the following day as showing 100 per cent hemolytic streptococcus. The blood culture was reported

negative. Sulfanilamide therapy was commended (t.i.d.) and repeated doses of pituitrin were administered in an effort to empty the uterus. Forty-eight hours later, placental fragments, still retained in the uterus, were evacuated by curettage. Cyanosis became very pronounced on the sixth day of treatment, so sulfanilamide was discontinued. Negative blood and cervical cultures were obtained the following day. She was discharged on the twenty-first day with normal pelvic findings.

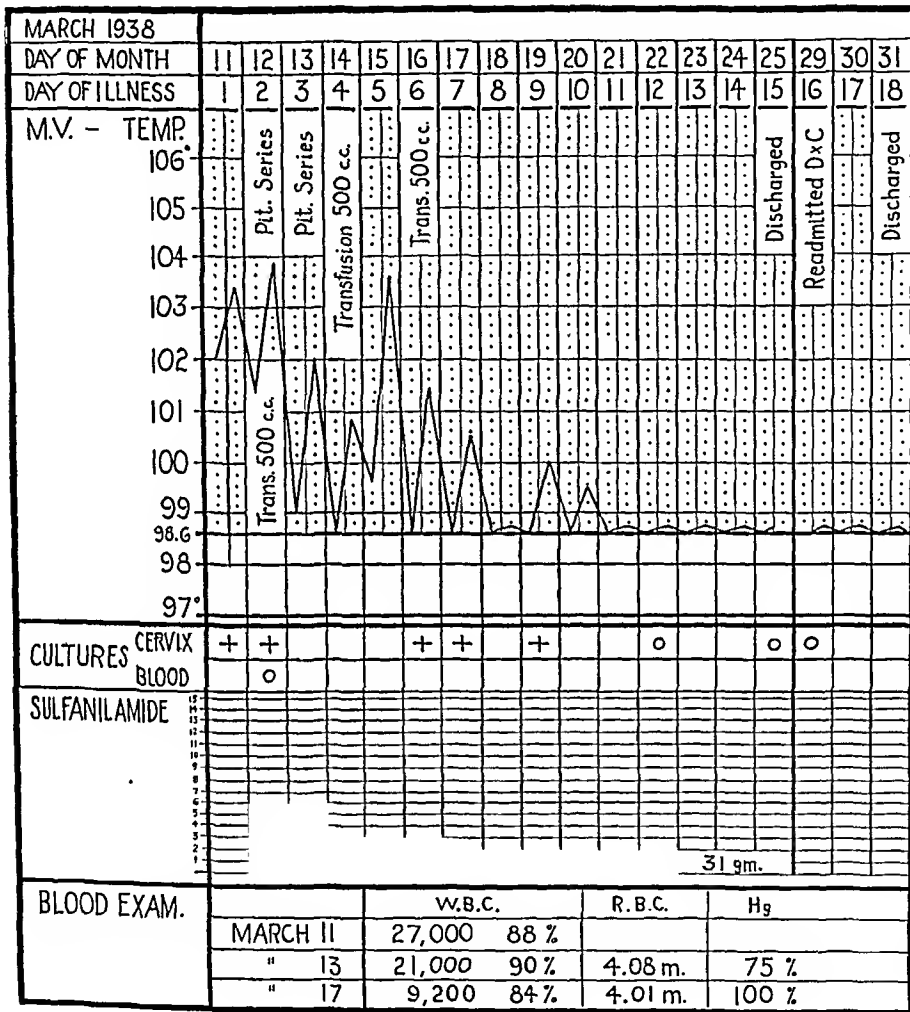


Fig. 2.—Case 2.

CASE 2.—M. V., a 27-year-old, married, white woman, gravida vi, para ii, was admitted on March 11, 1938, in the third month of pregnancy, complaining of slight vaginal bleeding for eight weeks. Increased bleeding followed by the passage of the ovum had occurred twenty-four hours before, after which she began to have chills and fever. Her three previous abortions were said to have been spontaneous.

Examination on admission showed the patient to be acutely ill, tenderness being present in the lower abdomen. Pelvic examination showed a patulous cervix with slight bleeding. Because of marked parametrial tenderness and thickening the uterus could not be defined clearly.

The uterus was soft, enlarged, and movable. The adnexa and parametrium were negative except for tenderness. Culture from the cervix was reported on the following day as showing 100 per cent hemolytic streptococcus. The blood culture was positive. Sulfanilamide therapy was commenced (t.i.d.). After twenty-four hours it was necessary to resort to the parenteral route because of uncontrollable vomiting. Repeated doses of pituitrin failed to cause expulsion of the sac; this was removed by curettage forty-eight hours after the initiation of chemotherapy.

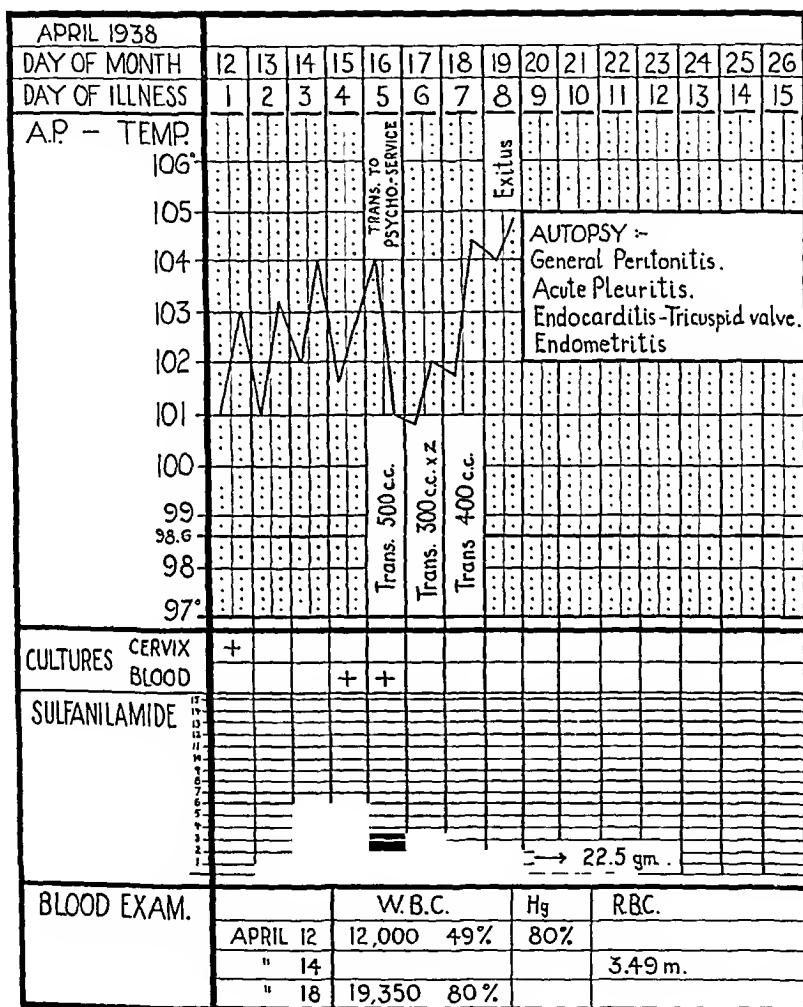


Fig. 4.—Case 4.

Her course continued uninfluenced by treatment, marked by high fever, and uncontrollable vomiting until her death on the ninth day.

The main findings at autopsy are noted on the chart.

CASE 4.—A. P., a 25-year-old, married, white woman, gravida vii, para iv, was admitted during the third month of pregnancy on April 11, 1938, complaining of chills and fever for two weeks, and vaginal bleeding for ten days.

On examination she appeared acutely ill; the abdomen was distended and tender. Pelvic examination showed the cervix firm, closed, with a slight bloody discharge. Extensive parametritis was present so that the uterus could not be outlined. Cervical culture was reported the following day as showing 100 per cent hemolytic streptococcus. Blood cultures were later reported as positive. Sulfanilamide was given first by the oral route (t.i.d.) but later the parenteral route had to be adopted

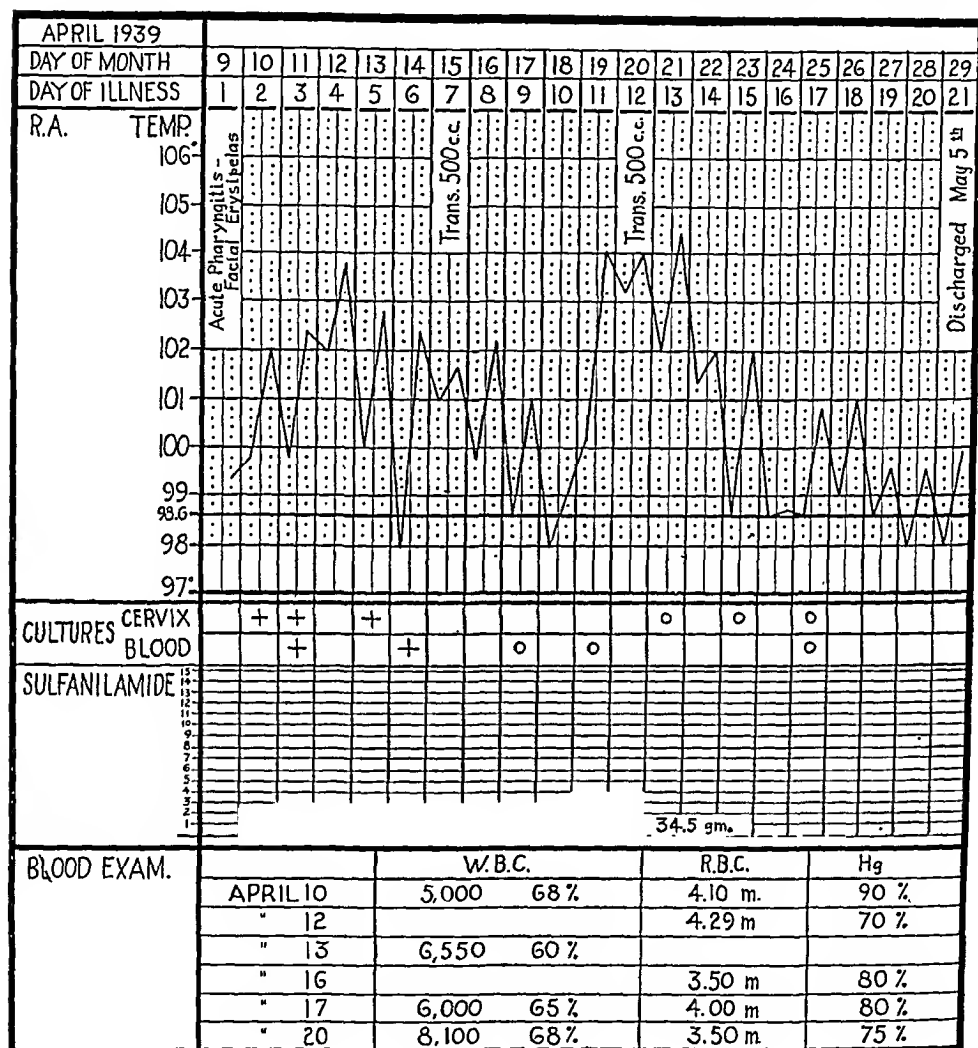


Fig. 5.—Case 5.

because of vomiting and delirium. The latter symptom made it necessary to transfer her to the psychiatric service. In spite of treatment her course continued unchanged, marked by evidence of general peritonitis, delirium, and high fever until her death on the eighth day. The main findings at autopsy are noted on her chart.

CASE 5.—R. A., a 35-year-old, married, white woman, gravida iii, para iii, was admitted as a post-partum patient on April 7, 1939. Forty-

CASE 9.—M. M., a 19-year-old married, white woman, gravida iii, para iii, was admitted on March 3, 1940, four days after a spontaneous, premature labor and delivery at home, complaining of lower abdominal pain, chills, and fever. She appeared acutely ill with tenderness over the lower abdomen.

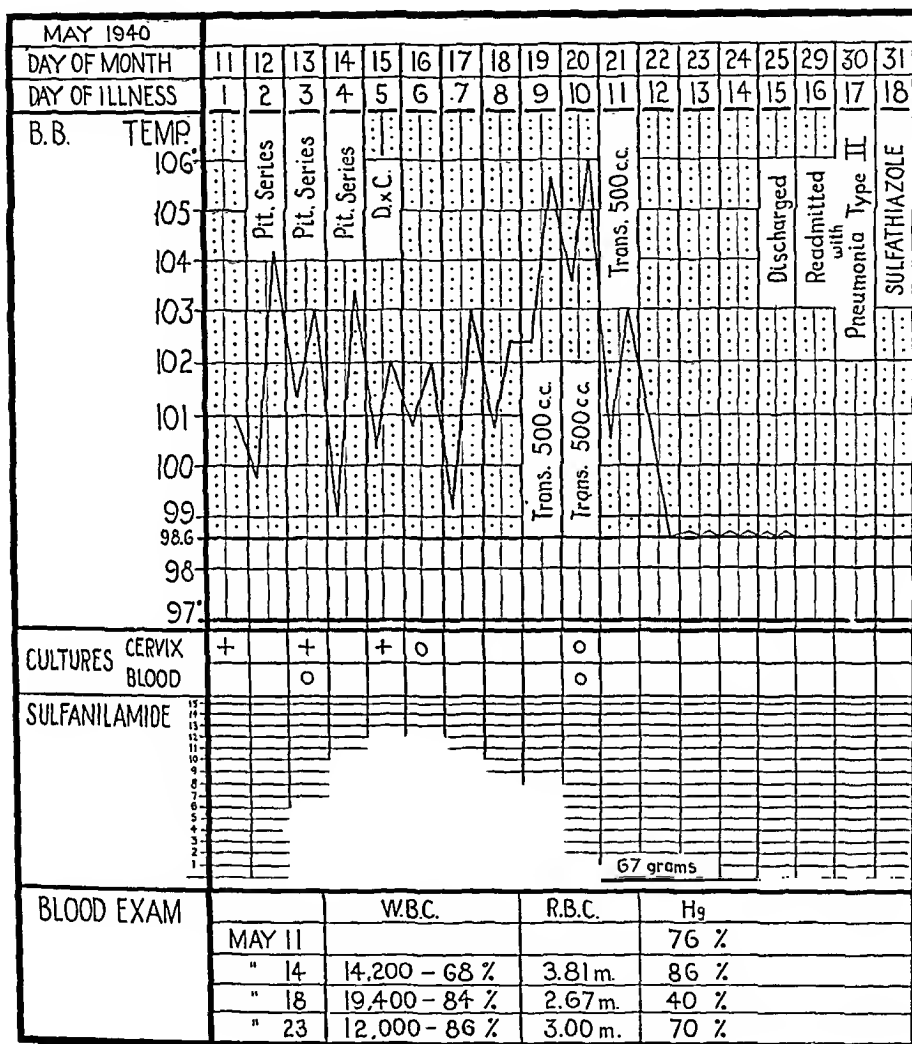


Fig. 10.—Case 10.

Pelvic examination showed a patulous cervix; the corpus uteri was enlarged, slightly tender, firm, and reached a point about 5 cm. above the symphysis. The adnexa and parametrium were negative. The cervical culture was reported the following day as showing 100 per cent hemolytic streptococcus. Blood cultures were negative. Sulfanilamide therapy was ordered (every four hours day and night). Rapid improvement ensued, negative cervical cultures being obtained on the sixth day of treatment. Patient was discharged on the ninth day with normal pelvic findings.

CASE 10.—Mrs. B. B., a 27-year-old, married, white woman, gravida iv, para ii, was admitted on May 11, 1940, in the second month of preg-

nancy, complaining of vaginal bleeding and lower abdominal cramps of several days' duration. She appeared acutely ill, and tenderness was present in the lower abdomen.

On pelvic examination the cervix was found to be soft and patulous with a bloody discharge; the corpus uteri was about the size of a ten to twelve weeks' pregnancy. No parametritis was present but slight tenderness was noted. Cervical culture was reported as showing 100 per cent hemolytic streptococcus. The blood culture was negative. Sulfanilamide therapy was begun forty-eight hours after admission

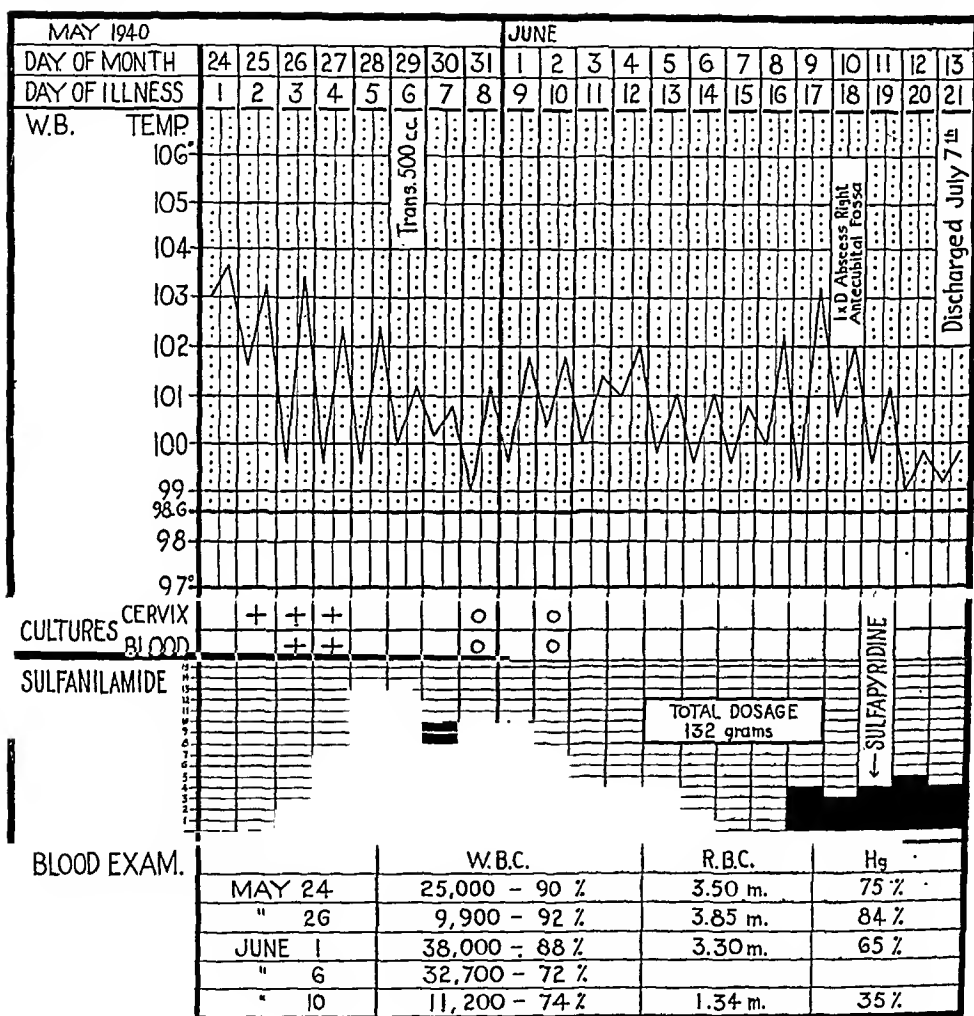


Fig. 11.—Case 11.

(every four hours day and night). Repeated injection of pituitrin failing to evacuate the ovum, this was accomplished by curettage on the fifth day. Rapid improvement followed, negative cultures being obtained on the sixth day. Fever, however, instead of decreasing reached higher levels but promptly disappeared on discontinuing chemotherapy.

The patient was discharged on the fifteenth day with normal pelvic findings. Four days after discharge she was readmitted with lobar pneumonia (Type II pneumococcus) and made a rapid recovery, being treated with sulfathiazole.

CASE 11.—W. B., a 25-year-old, colored female, was admitted on May 24, 1940, because of her previous history, to the tuberculosis service, despite her complaint of severe lower abdominal pain, fever, and vaginal bleeding, which occurred suddenly after three months' amenorrhea. After twenty-four hours she was transferred to gynecologic service. She was acutely ill, the abdomen showing every clinical evidence of general peritonitis.

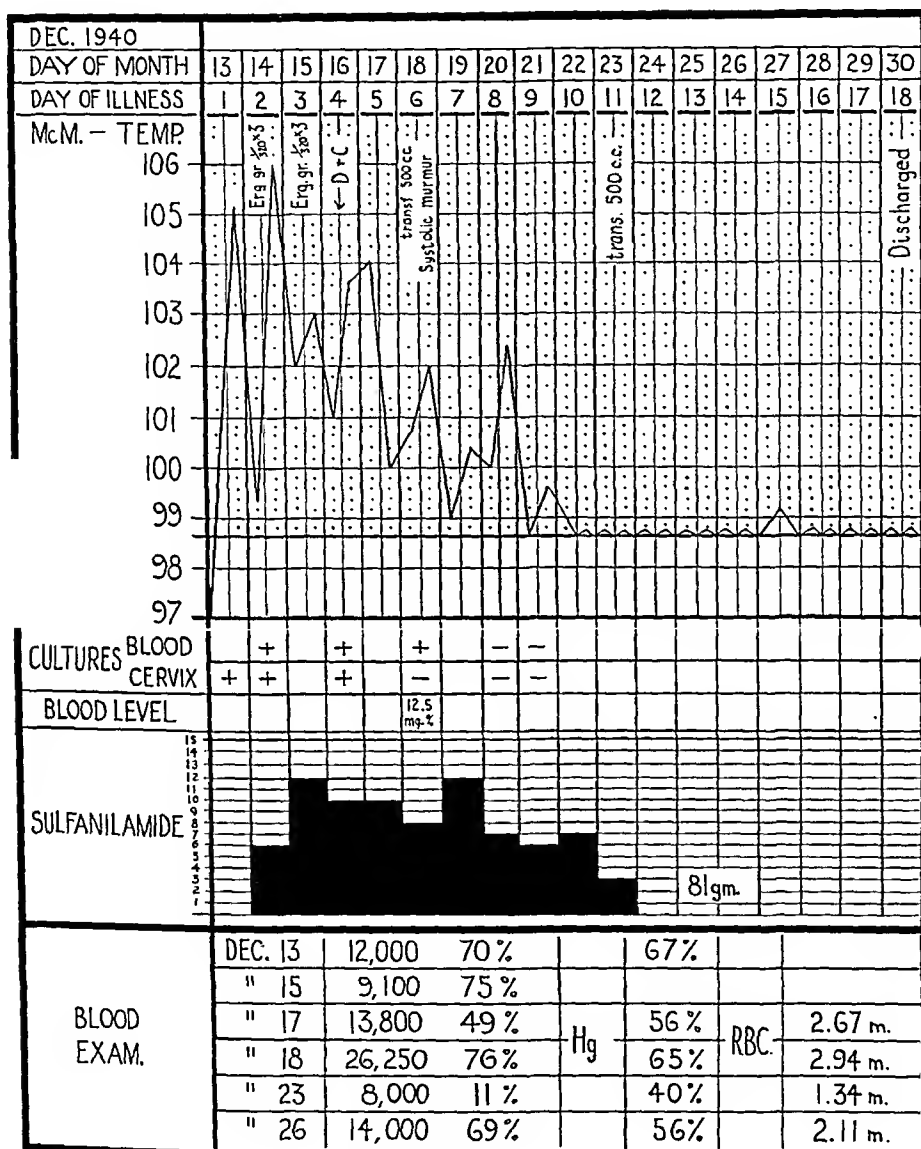


Fig. 12.—Case 12.

On pelvic examination the cervix was closed with a bloody discharge; the corpus uteri was enlarged to the size of a six to eight weeks' gestation. Extensive bilateral parametrial thickening and tenderness were present. The cervical culture was reported the following day as strongly positive for hemolytic streptococcus (Group A), the blood culture being reported as positive. Sulfanilamide therapy by the parenteral route

(every four hours for 6 doses) was commenced. In forty-eight hours, because of clinical improvement, the oral route was adopted. Blood and cervical cultures became negative by the sixth day of treatment. Fever continued to be present, apparently because of a tender, indurated swelling in the right anteeubital fossa at the site of an infusion. This area was drained on the twenty-first day, following which her temperature fell to normal. At this time sulfapyridine was substituted for a few days because the character of the pus suggested a staphylococcus infection. When the culture showed hemolytic streptococcus, small doses of sulfanilamide were resumed for about two weeks until the drainage tract became sterile. Patient was discharged on the thirty-seventh day, at which time slight parametrial thickening was the only abnormal finding.

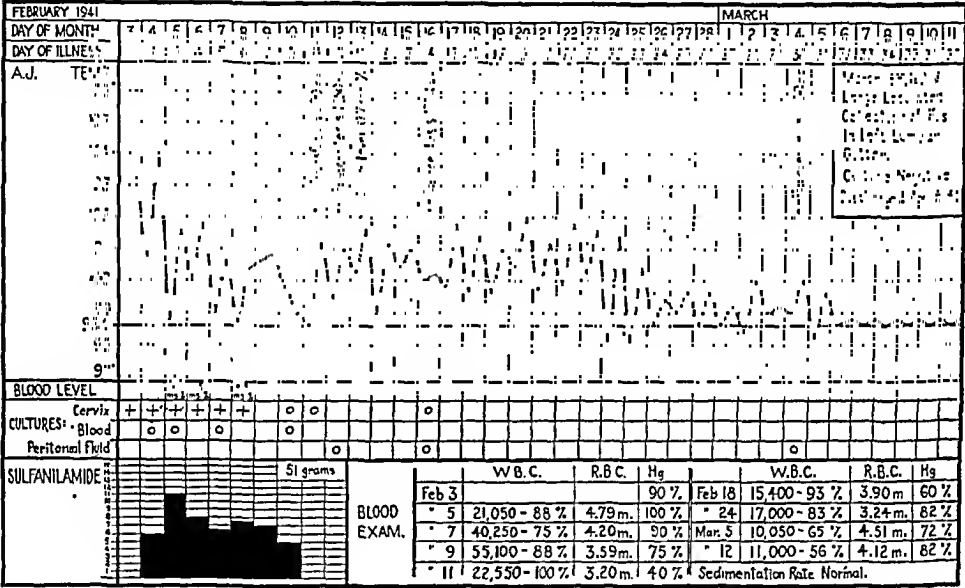


Fig. 13.—Case 13.

CASE 12.—McM., a 22-year-old, single, colored woman, gravida v, para ii, was admitted on Dec. 12, 1940, complaining of pain in the lower abdomen and vaginal bleeding of twenty-four hours' duration, occurring at the tenth week of pregnancy. She was not acutely ill at first, within twenty-four hours fever rose to 105° F. and pulse to 140. Moderate lower abdominal tenderness was present.

Pelvic examination showed a cervix which was soft and patulous; the corpus uteri was enlarged to the size of a three months' pregnancy. The cervical culture was reported on the following day as strongly positive for hemolytic streptococcus (Group A). The blood culture also proved positive. Sulfanilamide therapy was instituted (every four hours day and night). Repeated doses of ergotrate failing to completely evacuate the ovum, the placental remnants were removed by curettage in forty-eight hours. Blood cultures rapidly became negative, the cervical culture becoming negative on the seventh day of treatment.

Patient was discharged on the eighteenth day with normal pelvic findings.

CASE 13.—A. J., a 15-year-old, single, colored girl, gravida i, para 0, was admitted on Feb. 4, 1941, because of vaginal bleeding and lower abdominal pain of thirty-six hours' duration, following the induction of abortion at the sixteenth week of pregnancy. The fetus and placenta had been expelled eighteen hours before admission. She was acutely ill, the abdomen showing every clinical evidence of general peritonitis.

Pelvic examination showed a soft, closed cervix with a bloody discharge, the corpus uteri could not be made out, and induration with tenderness was present in the right parametrium. Cervical culture was reported the following day as showing 100 per cent hemolytic streptococcus (Group A). Blood cultures were negative. Sulfanilamide (every four hours day and night) was given by the parenteral route. Marked improvement took place, so that on the fifth day the oral route could be used, and, on the seventh day chemotherapy was discontinued because of negative cervical cultures. Negative blood cultures had been obtained previously. Blood level readings (performed in two laboratories) were unexplainably low during this time. Although nausea, vomiting, pain, and abdominal rigidity disappeared, fever persisted, and distention progressively increased to a point at which respirations were embarrassed. On the eighth day fluid could be demonstrated in the abdomen, mainly on the left side. On the tenth day 1,250 c.c. of sterile, dark amber fluid, containing fibrin and leucocytes, was removed by paracentesis under local anesthesia. It showed a sulfanilamide level of 0.7 mg. per 100 c.c., possibly due to the novocain used in the procedure. Four days later a second paracentesis was performed, because of rapid re-accumulation of fluid, with the removal of 1,250 c.c. of a similar fluid. Sixteen days later, a third paracentesis was performed, 1,650 c.c. of sterile fluid, containing a much larger proportion of fibrin and leucocytes, being obtained. Meanwhile fever had diminished and patient was allowed out of bed. Two weeks later, because of re-accumulation of fluid, incision and drainage of a large loculated space in left lumbar gutter resulted in the removal of a large quantity of sterile, thick, cloudy fluid containing large masses of fibrin. Drainage gradually ceased and she was discharged on the sixty-fourth day, still showing slight parametrial thickening.

Patient was seen one month later, when the pelvic and abdominal findings were normal, and she has remained well.

DISCUSSION

Several points deserve emphasis in the discussion of this small series. It is self-evident that this type of infection is uncommon at the present time. All of the cases mentioned, both those observed before and after 1936, occurred between early November and late May, the season when such infections are common elsewhere in the human body. Eleven of them occurred in patients suffering from abortion, some of them admittedly, and all of them presumably, induced. The remaining two represent infections occurring in post-partum patients, who delivered normally at home. In one of these the mother developed an extra-genital hemolytic streptococcus infection before delivery (Case 5). The circumstantial evidence in this group as a whole bears out strongly the

present belief⁴ that such organisms are conveyed to the parturient genital tract from some extragenital septic focus.

Bacteriologic diagnosis was the main basis for treatment in this group, and was made, in all cases, within twenty-four hours of admission to the gynecologic service. Cervical cultures on blood agar plates were taken on all cases of abortion with fever or suspected infection encountered during this period. The plates were immediately placed in a small incubator on the ward and read grossly in fifteen to twenty hours, thus avoiding the delay inherent in the transfer of such cultures to a central laboratory. The finding of predominant fine colonies with a wide zone of hemolysis was considered presumptive evidence of the hemolytic streptococcus. If, in addition, the patient showed clinical evidence that a severe infection was present, chemotherapy was immediately instituted. The plates were then sent to the bacteriologic laboratory for more exact study, and, sometimes, for classification of the organism.

Sulfanilamide was used throughout this series, because these infections were rare, and it was considered desirable to learn the effect of one agent before utilizing others. It is gratifying to note that some observers still consider this drug to be the most valuable of the sulfonamides in the treatment of hemolytic streptococcus infections.^{5, 6} At first relatively small doses were administered three times a day, mainly because of fear of toxic effects. Treatment was stopped for rather harmless manifestations, such as cyanosis. During this period the only two failures occurred (Cases 3 and 4). While there may be criticism of the inadequate chemotherapy received by the latter patients, it is to be noted that one of them was sick with fever for two weeks before admission and that both presented thrombotic lesions at autopsy which are notoriously resistant to chemotherapy.

Beginning in 1939, largely because of the pharmacologic investigations of Marshall⁷ and his associates, the drug was given six times a day at four-hour intervals, and, losing fear of the toxic effects, in gradually increasing quantities. During the past year, 12 Gm. a day have been given to patients with septicemia and, after forty-eight to seventy-two hours, the dosage has been gradually diminished. In severe local infections, the initial dose often has been smaller, consisting of 8 Gm., this quantity being diminished after forty-eight to seventy-two hours. These doses may appear large, but it must be borne in mind that many of these patients were desperate cases, in whom early and continued high concentration of the drug was important in the treatment of the disease. Serious toxic effects have not been noted, although they are to be expected in the future. One can discount the occasional occurrence of an idiosyncrasy to the drug, particularly in patients with septicemia, in whom the mortality, if untreated, is 88 $\frac{1}{3}$ per cent.

Many of these patients have had unpleasant side reactions, such as cyanosis, mental confusion, and nausea which proved merely transitory phenomena limited to the period of treatment. A pronounced leucopenia was observed only in one patient (Case 12). In most patients an anemia appeared. Whether this was due to the infection, or to the drug, is unknown but in all likelihood both factors played a part. This complication was successfully combated by transfusion, repeated as often as was indicated.

The oral route of medication was used wherever possible. When this route was made inefficient by vomiting, sodium sulfanilamide (5 per cent) was administered by the parenteral routes, the oral route being resumed as soon as it became practical. Equal doses of bicarbonate of soda have been given with the drug, because it was felt that this lessened the gastric disturbances, which sometimes accompany its use. In the latter part of the series, all forms of treatment involving puncture wounds by needles were reduced to a minimum, particularly when septicemia was present, because of the secondary abscesses occurring in Cases 7 and 11. In the latter case, the abscess in the antecubital fossa was far more troublesome than the primary uterine infection.

It was found that surgical evacuation of the uterus could be performed with relative safety after adequate sulfanilamide therapy had been in force for forty-eight hours (Cases 1, 5, 7, 10, and 12). It is believed that this procedure, when indicated by retention of placental fragments, is of importance in the early elimination of organisms from the uterus. Such a procedure was carried out in one of the fatal cases (Case 3) but, bearing in mind the chemotherapy which may have been inadequate and the findings at autopsy, it seems doubtful that the operation was necessarily related to the outcome.

It is to be regretted that blood levels were not carried out in all of these patients during treatment. However, the blood level in Case 12 certainly appears adequate, while those obtained in Case 13 are unexplainably low in spite of what appears to be a very ample dose of the drug. Such readings, during the use of a drug as uniformly absorbed as sulfanilamide, appear to be more of academic interest than of practical value in carrying out the treatment.

During the early part of the series treatment was continued, often with diminished doses until fever dropped to normal. Among those patients were three (Cases 5, 8, and 10) who developed secondary elevations of temperature, which promptly disappeared once chemotherapy was abandoned. These were all believed to be examples of drug fever. In all three, negative blood and cervical cultures had been obtained before the secondary fever occurred. A study of this series suggested that chemotherapy might be stopped on the basis of a negative culture from the cervix. As a precautionary measure, two successive negative

cultures might be required. In no instance did a cervical culture become positive after chemotherapy was discontinued. It is believed that evidence of bacteriologic cure is a much more efficient gauge for the length of treatment than the disappearance of fever. This was witnessed in the patient in Case 13, who continued to run a fever for twenty-three days after chemotherapy was discontinued, in spite of the fact that repeated cultures from blood, cervix, and peritoneal fluid failed to demonstrate organisms.

The result of chemotherapy, aided by the above-mentioned medical and surgical procedures, has been excellent except in the fatal cases (Cases 3 and 4). In the others, evidence of septicemia, when present, rapidly disappeared; the cervical cultures became negative in about a week except in Cases 2 and 6, in both of which organisms could be demonstrated for a somewhat longer period of time. It was felt that the fact that Case 2 was an unrecognized incomplete abortion might explain the persistence of uterine organisms. The late development of septicemia was conspicuous by its absence. Parametritis, except when present on the initial examination, has been absent. When present on admission, it has disappeared rapidly, the findings on almost all these patients being normal at discharge.

Among 13 patients, there were 2 deaths, a mortality of 15.4 per cent. However, if one merely considers the eight patients with septicemia or general peritonitis, or both, the mortality is 25 per cent. The latter group is comparable with the 12 cases seen prior to June, 1936, when chemotherapy was not available, with a mortality of 83½ per cent. This is a tremendous improvement which, it is hoped, may be made still better in the future.

Before closing, it seems worth while to call attention to the fact that chemotherapy may so alter the course of disease as to produce the unusual clinical picture observed in Case 13. Here, in spite of every evidence that a bacteriologic cure had been obtained, surgical drainage became necessary to eliminate a recurring localized peritoneal exudate.

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A COMPARATIVE STUDY OF TUBAL INSUFFLATION AND LIPIODOL INJECTION IN STERILITY

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I HAVE endeavored in the following article to present comparison of the indications, merits, and relative morbidities attending tubal insufflation and uterosalpingography. As an actual fact, however, the question is not so much one of preference between the two methods, as of defining the place for each in the diagnosis and therapy of female sterility. The results of personal experience in the use of these procedures in 706 patients are presented. Included are two deaths, one following each procedure.

One of the most valuable additions to the diagnostic armamentarium of the gynecologist in recent years was made in 1920, when Rubin¹ published his first observations on the nonoperative determination of the patency of the Fallopian tubes by means of intrauterine inflation with oxygen and the production of an artificial pneumoperitoneum. Since then, the principles suggested by Rubin have become more widely adopted in the investigation of female sterility and diseased conditions of the Fallopian tubes; and, from having at first purely diagnostic significance, it has come later to be recognized as possessing definite therapeutic value. Considerable variation and modification have taken place in the technique of the procedure since it was first proposed by Rubin.

During the same period, uterosalpingography was developed and soon rivaled the use of tubal insufflation. W. H. Carey,² in 1913, first proposed and described a method of testing the patency of the Fallopian tubes by the use of collargol and the subsequent roentgenologic demonstration of its presence in the peritoneal cavity.

Simultaneously with Carey, Rubin experimented with collargol solution and later other radiopaque media to demonstrate the patency or obstruction of the Fallopian tubes. Kennedy,³ in 1923, used a 20 per cent solution of sodium iodide for the same purpose.

In 1921, C. Heuser⁴ recommended the use of lipiodol and soon after others confirmed the advantages of this solution. At present, lipiodol has displaced other media in the x-ray visualization of the lumina of the uterus and tubes.

Of the two procedures, gas insufflation is the simpler and less expensive. Further, carbon dioxide is completely and harmlessly absorbed within a few hours. On the other hand, in the author's personal experience, as well as will be later indicated by review of the literature, lipiodol has been shown to remain for months and even years in the

peritoneal cavity or in the lumen of the tubes. There has been a considerable difference of opinion as to the harmfulness or innocuousness of residual lipiodol. This oil, although usually nonirritating, is a foreign body and may produce foreign body reaction in the tissues.

Among the advantages claimed for insufflation are: (1) It seems logical to assume that kinking of the tubes may be corrected by the forcible passage of gas through them; (2) Isthmospasm may be overcome; (3) Stricture of the tubes may be forcibly stretched; (4) Fimbrial adhesions may be broken up.

MORTALITY

One of the most serious, though fortunately very rare hazards of tubal insufflation is the possibility of air embolism and sudden death. Among the fatal cases which have been reported, are the following:

CASE 1.—(G. L. Moench.⁵) Rubin test: Tubes found closed. A dilatation and curettage immediately was performed under light anesthesia, during which the patient suddenly collapsed and died in a few minutes without any apparent cause, since the heart, lungs and kidneys had been found surgically competent. Autopsy a few hours later showed: Heart normal, except that the right heart contained numerous gas bubbles which were also present in the inferior vena cava. Genital organs were normal except for the right tube which contained blood and gas bubbles. Cause of death: Embolism due to gas insufflation followed by dilatation and curettage. The important contributing factor to this death was the curettage which was definitely contraindicated following gas insufflation.

CASE 2.—(G. L. Moench.⁵) Heart and lungs were normal; gynecologic examination was negative. Tubal insufflation was performed using oxygen. Patency was established with a pressure of 200 mm. of mercury. Following the flow of gas, the patient suddenly collapsed and died in a few minutes. Autopsy: Upon opening the abdomen, escape of gas occurred, and the cavity was found filled with turbid yellowish fluid. A small tear was found in a loop of small intestines in the pelvis. The Fallopian tubes appeared normal. A small red spot was found on the posterior surface of the uterus. The veins on the posterior surface of the left ventricle contained small gas bubbles. Anatomic diagnosis: (1) Gas in veins of heart, and gas in abdomen; (2) perforation of small intestines; (3) perforation of uterus (?). Cause of death: Postoperative shock following oxygen insufflation.

CASE 3.—(J. H. Dibble et al.⁶). Patient, age 41 years, had primary sterility; pelvic examination was negative. During a tubal insufflation with gas at level of 150 to 200 mm. of mercury; total volume of air used, 150 c.c.; patient suddenly became cyanosed and respirations ceased. The heart was beating rapidly but feebly. Death occurred within four minutes in spite of cardiac stimulants and artificial respiration. Autopsy findings: Uterine veins, inferior vena cava, right auricle and ventricle, pulmonary artery, and its main branches were all filled with air bubbles. Death was attributed to air embolism. These authors have dis-

cussed the mechanism of death from air embolism in a most comprehensive fashion and have surveyed the literature on the subject.

CASE 4.—(O. P. Mansfield and A. Dubits.⁷) This was a case of fatal air embolism following perturbation. Mansfield and Dubits attribute the fatality to the presence of an undiagnosed tuberculous endometritis. The caseous tissue yielded under the pressure of the air and permitted its entrance into a vein.

CASE 5.—Weitzman⁸ reported a similar mortality following tubal insufflation. During the test, the patient developed a convulsive seizure, with gradual onset of coma. Autopsy diagnosis: Air embolism.

Rubin has emphasized that air embolism is best prevented by rigidly avoiding the test during the premenstrual period, when the endometrium is in a congested state, or when uterine bleeding of any form is occurring. Further reasons for avoiding this bleeding state are the risk of blowing detached fragments of endometrium along the tube with subsequent danger of endometriosis. There is also the possibility that the premenstrual swelling of the endometrium might be of such degree as to hinder the passage of gas into the tubal ostia and produce a condition resembling tubal obstruction. Rubin has indicated that 200 mm. of mercury is to be regarded as the upper limit of safety to avoid the danger of tubal rupture. Ferguson⁹ reports a case in which with the patient under anesthesia and the abdomen opened, air was deliberately injected into a hydrosalpinx. He observed a rupture of the tube at a pressure of 250 mm. of mercury.

MORBIDITY FOLLOWING TUBAL INSUFFLATION

A survey of the literature has revealed the following reports on cases of insufflation and salpingography (Table I).

TABLE I

AUTHOR	NO. CASES	SYNCOPE		PELVIC IRRITATION OR INFECTION	
		SLIGHT	SEVERE	SLIGHT	SEVERE
Rongy ¹⁰	400		1		4
Rubin ¹¹	3600	34			
Mayer ¹²	406			1	
Feiner	541			3	

Loomis¹³ reported no morbidity in 732 cases, and Goodall¹⁴ in 500 cases. Thus, in a total of 6,183 cases of tubal insufflation, syncope was noted in 35, an incidence of 0.6 per cent; and pelvic irritation or infection in 8, an incidence of 0.1 per cent. These figures indicate the scarcity of complication. Actually, as can be seen from Table I, severe morbidity of any type was seen in only 5 patients in the entire group, a frequency of less than one in one thousand.

MORBIDITY AND MORTALITY FOLLOWING UTEROSALPINGOGRAPHY

There is evidence of greater mortality and morbidity following uterosalpingography than following tubal insufflation. The literature is replete with reports of initiated or reactivated pelvic inflammation. Many authors have carefully studied the gross and microscopic changes induced by this procedure, and others have noted evidence of uterovenous reflux of lipiodol. Some animal experimentation has also been done. The most important of these reports and studies are shown in Table II.

TABLE II. PELVIC INFLAMMATION AND DEATH FOLLOWING UTEROSALPINGOGRAPHY

AUTHOR	NO. CASES	OPAQUE MEDIA	PELVIC INFLAMMATION		TUBO-OVARIAN ABSCESS	PELVIC ABSCESS	CHRONIC TUBO-OVARIAN DISEASE	DEATHS
			MILD	SEVERE				
Randall ¹⁵	600	Lipiodol	3					
Rubin ¹⁶	150	Lipiodol	2	3	2	1	2	
Lecène, Tedesco, and Beclere ¹⁷	230	Iodine oil		1				
Gauss ¹⁸ (collected)	3,000	Iodine oil		13				5
Schultz ¹⁹ (collected)	8,000	Iodine oil		27				3
Wilson ²⁰	57	Lipiodol				1		
Schneider ²¹	200	Lipiodol		1				
Schultz ¹⁹	400	Iodopin						
	200	Lipiodol	5					
Cotte and Martin ²²	250	Lipiodol						
Feiner	337	Lipiodol	4	2		1		1

Morbid reactions following the injection of iodopin or lipiodol have also been reported by Bisengeler,²³ Odenthal,²⁴ Hoffman,²⁵ Sieard,²⁶ Douay,²⁷ Brun and Cortesi,²⁸ Schroeder and Jacobi.²⁹

In the total group of 13,424 cases in the above table, pelvic inflammation was noted subsequent to uterosalpingography in 68, an incidence of 0.5 per cent, five times that for tubal insufflation.

There is evidence to indicate the presence of contrast oil at laparotomy after salpingography.

Schultz¹⁹ reports a series of 200 cases in which laparotomy was performed one to six days after salpingography. A frequent finding was a thin shiny film of the contrast oil on the surface of the Douglas peritoneum. He observed neither evidence of irritation of the latter, nor any fresh adhesions. Iodine-containing masses found at laparotomy following salpingography have been reported by Kustner,³⁰ Lash,³¹ and Ries.³² The author has had the opportunity of operating after salpingography only once, but in this case too, gross pathologic changes due to the irritation of the oil were noted. This case will be described in some detail later.

On the other hand, several investigators have failed to confirm these findings.

Werner-Volk³³ reported a series of 91 cases of laparotomy performed several days after hysterosalpingography. There were no structural changes due to the oil, and further, there were no unusual postoperative febrile reactions. In the vast majority of patients, the conclusions drawn from the roentgenogram pictures, regarding the permeability of the tubes and the kind and the localization of the obstruction, were proved to be correct. K. Wilson²⁰ has done several abdominal operations after the introduction of lipiodol and noted no signs of peritoneal irritation even though the lipiodol was still present in the pouch of Douglas. G. Cotte and Martin²² reported observations during many laparotomies in patients examined with this medium, either immediately afterwards, or twenty-four to forty-eight hours later, and he has never found any signs of inflammation or irritation of the peritoneum.

There is only slight evidence for microscopic changes due to this procedure.

Rubin¹⁶ mentions three characteristic pathologic findings following oil injection; inspissation, foreign body giant-cell infiltration, and closure of the tubal lumen. He noted the lesion to be almost identical with that produced by gonorrhea (salpingitis nodosa) and tuberculosis, from which it must be differentiated. In the author's case already alluded to, similar histologic changes were noted.

The weight of evidence, however, is against such histologic changes. Zimmerman and Nahmmacher³⁴ observed no evidence of changes in the histologic study of the epithelium lining the tubes or any evidence of oil rests in patent tubes. In closed tubes, changes could be found which antedated and had no relation to the injection. Cotte and Martin²² expressed the same opinion in the histologic examination of ten cases of extirpated tubes; and similar observations were reported by Jung³⁵ who also examined the uterine mucosa. Schroeder²⁹ reported a case in which microscopic examination one year after lipiodol injection revealed oil still present in a closed tube without causing any fresh inflammatory reaction. In Stoeckel's clinic, Schultz¹⁹ examined twelve cases for changes in the uterine mucous membrane. Only one case showed any endometritis and this was in connection with a subserous tumor. Schultz concluded as follows: In normal tubes the mucous membrane shows no change; chronically involved tubes, which are already in the healing stage, show no change; however, if residual inflammation is still present, it is very likely to be reactivated. The histologic examination of extirpated tubes and endometrium in a series of 91 cases of Werner-Volk³³ proved that no inflammatory reaction was present when all precautions as to the oil injection had been taken.

Among the possible complications of salpingography is accidental injection of iodized oil into the uterine veins.

Meaker³⁶ mentions two theoretical explanations: The first is a dissolution of continuity of the endometrium, the result of functional desquamation, neoplastic change of operative trauma; second, excessive pressure may force oil through the epithelial layer, even though this be intact or normal; and third, the explanation advanced by Witwer and associates,³⁷ namely, that abnormal permeability of the endometrial tissue exists, as an idiosyncrasy, in a certain few women. In most cases

this accident appears to produce no ill effects. In a case reported by Meaker³⁶ and in two cases of my series, there were no disturbing reactions of any kind. Similar observations have been reported by Effke-mann,³⁸ Witwer,³⁷ Coventry,³⁹ and Wang⁴⁰ and others. B  el  re⁴¹ observed such a uterovenous reflux in a test following bilateral salpingectomy, Solal⁴² in the presence of an infantile uterus, Petit-Dutaillix,⁴³ immediately following an injection of 12 c.c. of iodopin. That more serious consequences, however, may result from this accident are shown by the case reports of Hemmeler,⁴⁴ and Brull and associates,⁴⁵ of pulmonary embolism occurring within twenty-four hours following the test. Both patients recovered.

Zimmerman and Nahmmacher³⁴ did a series of experiments in which lipiodol was injected into the tubes of laboratory animals. The only change they observed was the formation of oil deposits in the peritoneum. There was no evidence of inflammatory reaction; only fibrin, leucocytes, and imprisoned oil were noted. Schultz¹⁹ obtained similar findings following the injection of a series of rabbits and guinea pigs with iodopin or lipiodol.

CASE MATERIAL

Seven hundred and six patients were examined by the author; 464 were cases of primary sterility and 242 of secondary sterility. For the entire group, 5 were under the age of twenty years, 288 were between twenty and thirty years, 207 were between thirty and forty years, and 6 were over forty years of age. The period of sterility is shown in Table III.

TABLE III

	PRIMARY	SECONDARY	TOTAL
Under 1 year	32	44	76
1 year	87	28	115
2 to 5 years	235	115	350
6 to 10 years	100	54	154
Over 10 years	10	1	11
	464	242	706

One hundred and forty-eight patients gave a history of previous miscarriages, in 54 of whom the abortion was induced. One hundred forty patients presented other pertinent obstetric history. The largest number (103) had one child previously, while 11 had two or more children previously. In this group, 10 gave a history of puerperal infection. Sixteen patients were operated upon for ectopic gestation. The associated symptoms were principally menstrual irregularities and dysmenorrhea. In this group, 113 complained of irregular menses, 43 of oligomenorrhea, 18 of metrorrhagia, 13 of menorrhagia and 197 of dysmenorrhea. Dyspareunia was noted in 30 patients. There was a history of previous pelvic inflammatory disease in 41 cases, of which 15 were postabortal in type.

Twenty-six per cent, or 184, gave a history of previous surgical procedures. Appendectomy exceeded any other operation by far and was noted in 78 cases.

Constitutional defects that were considered as a possible cause for sterility were noted in 52 patients, 30 of whom had a past history of hypothyroidism, 13 of hyperthyroidism, 5 of tuberculosis, and 4 of diabetes.

Endometrial biopsy was performed in 36 patients; 6 showed interval mucosa, and 30 gave evidence of ovulation by exhibiting the premenstrual secretory changes. In 30 patients the general make-up was that of dystrophia adiposogenitalis.

A routine cheek-up of the husband revealed major contributing pathology in 25 per cent of the series.

Table IV shows the data found at pelvic examination.

TABLE IV

Erosion of cervix	77
Laceration of cervix	9
Laceration of cervix and perineum	6
Retroversion	73
Leucorrhea, nonspecific	87
Trichomonas	47
Intact hymen	6
Thickened adnexa	{ Unilateral 22
	{ Bilateral 11
Acute ante flexion	49
Cervical stenosis	19
Mucus plug	35
Ovarian cyst	6
Uterine fibroid	8
Infantile uterus	37
Marked prolapse	2
Double uterus and vagina	3

Various types of therapy other than insufflation given elsewhere and by the author are noted in Table V.

TABLE V

1. Dilatation of cervix	20
2. Dilatation and stem pessary	13
3. Cauterization of cervix	46
4. Local tampon treatments	71
5. Short wave treatments	56
6. X-ray stimulation	6
7. Dilatation and curettage and radium	2
8. Pessary	11
9. Dilatation and curettage	11
10. Excision of vaginal septum	7
11. Foreign protein therapy	10
12. Laparotomy for salpingostomy	10
	(5 cases—author)
	(5 cases—elsewhere)

Of these 10 salpingostomies, 2 were followed by pregnancy and 8 were unsuccessful.

TUBAL INSUFFLATION

Eight hundred and thirty-one insufflations were given to 541 patients. Of these, one insufflation was performed in 346 cases, 2 in 256 cases, 3

in 147 cases, 4 in 40 cases, 5 in 30 cases, and 6 in 12 cases. The status of the tubes as determined by this procedure was as follows: patent 262 cases, complete obstruction 192 cases, stenosis 60 cases, and spasm 27 cases.

Patency was established by the insufflation in 59 cases of tubal obstruction. The greatest number (39) occurred following one negative insufflation, 17 followed two negative insufflations, and 2 followed three negative insufflations. In another group of 29 patients in whom complete obstruction was determined by lipiodol visualization, patency followed tubal insufflation. In 16, the previous salpingogram had demonstrated bilateral cornual obstruction; in 9, bilateral fimbriated end obstruction; and in 4, a combination of the two types. The explanation here is probably that the lipiodol, owing to its thicker consistency, was unable to pass through the lumen of a stenosed but permeable tube.

PREGNANCIES FOLLOWING TUBAL INSUFFLATION

A total of 84 patients conceived following tubal insufflation. The time interval between the test and conception was as follows: One month, 25; two months, 19; three month, 16; four to six months, 17; seven months to one year, 7 cases. Of further interest is the fact that 50 pregnancies followed one insufflation, 30 pregnancies 2 insufflations, and 4 pregnancies 3 insufflations.

MORBIDITY FOLLOWING TUBAL INSUFFLATION

There were three mild pelvic irritations. One patient had some disturbance of uterine bleeding several weeks later with some small exudate in the posterior cul-de-sac; one patient bled moderately for two weeks and then the bleeding cleared up with bed rest; and one patient had amenorrhea for six months following insufflation.

CASE REPORT OF MORTALITY FOLLOWING TUBAL INSUFFLATION

This death occurred in the early days of tubal insufflation. The original Rubin apparatus and oxygen tank were used. The patient was a nullipara, 26 years of age, who had had a salpingo-oophorectomy two years previously. During the test, the pressure was allowed to rise to 160 mm. of mercury. The procedure was discontinued at this point because the patient complained of a smothering sensation. There immediately occurred a generalized convulsion followed by about a dozen convulsions during the course of one-half hour, at which time the patient died. The autopsy findings were as follows:

The body was that of a markedly obese white female, 5 feet 1 inch in height and weighing 170 pounds. No free fluid was noted in the abdominal or pleural cavities. The heart weighed 290 mg.; the ventricular and auricular walls were markedly atrophied and the posterior surface of the left ventricle showed a rupture of a coronary vein. There was free blood in the pericardial cavity. The lungs were voluminous in the upper lobes and markedly congested at the bases. The liver was markedly increased in size, showed large areas of fatty degeneration, but cut with marked resistance and was deeply congested. The spleen was also intensely congested and the pulp soft and pultaceous. The kidneys were deeply congested but the parenchyma, calices, and pelves

were normal. The genital organs were markedly adherent to the pelvic wall. The right tube and ovary were markedly thickened and the ovary cystic. The left tube and ovary were missing. The pathologic diagnosis was: Rupture of a coronary vein, hemopericardium, pulmonary thrombosis, and chronic myocarditis.

An opinion rendered by Dr. Louis S. Speeter, cardiologist, in connection with this death is as follows:

"This case appears to be most unusual in all respects, particularly the rupture of the coronary vein. A search through the quarterly cumulative index from 1940 back through 1927 reveals no mention of coronary vein rupture. The autopsy findings reveal some pre-existing disease since the ventricular and auricular walls were markedly atrophied, and the liver shows large areas of fatty degeneration. The rupture of the coronary vein may have occurred secondary to the convulsion regardless of the cause of the convulsion. By no physiologic or pathologic relation that occurs to me could a tubal insufflation directly bring about coronary vein rupture. Possible explanation as to the cause of the convulsion might include a pre-existing tendency to convulsion, epilepsy, air embolism or a parasympathetic stimulation causing slowing and perhaps temporary stopping of the heart bringing about something in the nature of a Stokes-Adams syndrome."

UTEROSALPINGOGRAPHY

Uterosalpingography with lipiodol was performed on 337 patients. One or both tubes were patent to this procedure in 188 and both were closed in 149 cases. In the first group of 188 patients, 69 showed evidence of unilateral tubal obstruction, 35 at the cornual end, and 34 at the fimbriated ends of the tube. The sites of bilateral obstruction in the second group were: bilateral cornual end, 68 cases; bilateral fimbriated end, 55 cases; combinations of the two, 23 cases, and obstruction and stenosis of a second tube in three cases.

Twenty patients showed patency to lipiodol visualization after a negative insufflation, probably due to isthmospasm.

During the course of these investigations, 102 cases, or about 30 per cent, showed functional uterine pathology or anomaly. This was thought to be a surprisingly high figure for such association. The following types were noted:

1. Spastic uterus, 33 cases.
2. Small uterus, 35 cases. In only 5 of these was complete obstruction noted.
3. Rudimentary uterus, 35 cases. In only 5 of these was complete obstruction noted.
4. Anomalies of development, 23 cases.
 - a. Uterus bicornis unicollis, 20 cases. In 7 of these complete obstruction was noted.
 - b. Uterus didelphys, 2 cases.
 - c. Uterus bicornis septus, 1 case.

MORBIDITY FOLLOWING LIPIODOL INJECTION

Six patients showed gross morbidity following uterosalpingography. Brief descriptions follow:

1. One febrile reaction reaching 102° F., patient in bed one week.

2. Left tuboovarian mass, 6 cm. in size, moderately tender. No fever. Mass disappeared in one month.

3. One bilateral oleosalpingitis, afebrile, moderately tender, disappeared three months later.

4. One unilateral salpingitis, no temperature, severe pain, incapacitated for one month. X-ray check in six months showed small residual shadow. Examination revealed small palpable mass which was moderately sensitive.

5. Bilateral tubal masses which required laparotomy four months following the oil injection; one tube removed, and second tube resected. Laboratory report: Several foreign body granulomas present, containing epithelioid cells, giant cells, lymphocytes; marked resemblance to histologic picture of tuberculosis.

6. Febrile reaction of 103° F., persisted for ten days. Pelvic abscess found which required posterior colpotomy; seventeen days in hospital. Examination one year later, uterus mobile; small exudate in posterior and both lateral fornices.

PREGNANCIES FOLLOWING LIPIODOL

A total number of 58 patients conceived within one year following this procedure. The intervening period was as follows: 11 cases, one month; 10 cases, two months; 13 cases, three months; 12 cases, four to six months; 12 cases, seven to twelve months.

CASE OF MORTALITY FOLLOWING LIPIODOL INJECTION

The patient was a 28-year-old nullipara. There was no history of pelvic infection and her last menstrual period occurred sixteen days prior to the test. On pelvic examination, there was no evidence of external infection. The cervix appeared normal and the body of the uterus was anterior, normal in size and mobile. There was no palpable adnexal pathology.

Lipiodol examination under the usual aseptic precautions showed a uterine cavity of normal size and contour. The right tube was obstructed only at the fimbriated end and the left tube showed free oil escaping from the fimbriated end. A twenty-four-hour x-ray plate showed an abundance of free oil in the pelvis. There were no unusual symptoms at this time, but two days later the patient developed cramplike pains in the abdomen and vomiting. A low-grade fever with the temperature never exceeding 101° F., accompanied by lower abdominal cramps was noted for the next twelve days, during which time the patient was confined to bed.

On the fourteenth day following the lipiodol injection, she was admitted to the Beth Moses Hospital with the clinical picture of generalized peritonitis. The abdomen was distended by a tender, boggy exudate which filled the entire pelvis. The leucocyte count was 18,400 with 88 per cent polymorphonuclears and the sedimentation time forty-five minutes. Within two hours after admission, the patient's pulse became rapid and thready, her body cold and clammy, and her nails and lips blue. The temperature rose to 105° F. and her pulse to 160; she died twelve hours after admission.

Necropsy showed the peritoneal cavity to be filled with a large quantity of greenish and brownish foul-smelling pus. The intestines were covered and matted together by a thick fibropurulent exudate, and on separation large pools of pus were disclosed. The serosa of the intestines showed focal areas of necrosis and the omentum was partially gangrenous. The lungs showed pulmonary edema and the heart was essentially normal. The liver was partially covered by the peritoneal exudate and showed moderate disturbance in its lobular structure and fatty infiltration. The spleen was slightly enlarged and softened. The kidneys and adrenals were essentially without changes. Examination of the pelvis showed marked congestion and numerous pin-point hemorrhages throughout the mucosa and the bladder. The uterus was of normal size and its endometrium showed moderate polypoid hyperplasia. The right tube and ovary were greatly enlarged and matted together. The fimbriated end of the tube was closed but section revealed a large amount of thick yellowish green pus. The left tube showed an essentially similar picture except for a perforation 6 mm. in diameter at the fimbriated end from which pus exuded. Smears of the pus showed gram-negative bacilli and gram-positive cocci in chains. Culture identified the organisms as *B. coli* and *Streptococcus non-hemolyticus*.

COMMENT

It would appear that this patient had pelvic infection despite the negative history and findings, and that the uterosalpingography was responsible for sufficient spread and exacerbation to cause a fatal peritonitis. A similar instance of pelvic infection without clinical evidence was reported by Dr. Joseph L. Baer⁴⁶ who opened the abdomen of an apparently normal patient free from elevation of temperature with the intention of doing a Gilliam suspension of the uterus, but in whom he found the tubes dripping free pus from the fimbriae. It occurred to him that tubal investigation in such a case would probably be followed by untoward effects. It is clear that it is possible, though not likely, to encounter active pelvic infection without obvious clinical findings for inflammation. The danger of uterosalpingography in such a case has already been forcibly demonstrated. The frequency of this condition is so rare, however, that it should not contraindicate lipiodol visualization. A careful history and pelvic examination, along with a leucocyte count and sedimentation time in doubtful cases, should decrease the risk.

DISCUSSION

The advantage claimed by those who favor lipiodol is the ability to localize definitely the site and the extent of the obstruction of the tubes. This is of the utmost importance in making the decision as to the proper selection of cases for the operative relief of sterility problem cases.

Rubin, however, has not only been able to determine the presence of tubal patency, stenosis, and spasm; but through the gradual development of his apparatus has been able to obtain the same information with less danger and discomfort to the patient. On the other hand, the changes in size and shape of the uterine cavity are of great value if

visualized. Considering that a large number of sterility cases are due to developmental anomalies not easily diagnosed by palpation, the roentgenogram furnishes great aid. Thus 30 per cent of this series of 337 cases showed some evidence of functional uterine pathology or anomaly of the uterus. The infantile uterus is a most common example, and well demonstrated, in its small capacity, holding about 1 to 2 c.c. of oil, and casting a very small triangular shadow. Likewise, the demonstration of markedly bicornuate structural outlines of the uterus, or filamentous rudimentary type of tubes is of great value. Occasionally unsuspected submucous tumors of the uterus may be diagnosed by the hystrogram. In cases in which insufflation already has shown adherent or stenosed, but permeable, tubes, lipiodol may not pass through because of its thicker consistency. Therefore, in those cases in which one or both tubes show partial occlusion, as demonstrated by an insufflation, lipiodol injection should be used cautiously as complete occlusion may result and thus defeat the primary objective.

Schultz states that he has never seen one case of closed tubes at laparotomy caused by the iodine oil filling, provided he did not observe inflammatory changes or closure on the previous x-ray plate. To prove this point, 200 cases were selected by Schultz in which the contrast filling was repeated two or three times. In none of these cases in which the original salpingography demonstrated patency was obstruction found in the second or third investigation.

By contrast, Hoffman²⁵ expresses his disapproval of the entire procedure of salpingography because of the danger of fresh infection, reactivation of old infections, or inflammatory processes; irritation of the tubes with consequent agglutination and adhesions; also, because of the retention of the contrast medium in the tubes which he considers to be by no means immaterial. Comparing the procedure with tubal insufflation, he concludes that the latter is a much more harmless method than salpingography. It would seem that this view is rational, but the untoward effects of uterosalpingography in properly selected cases should not be considered as excessive. One should not be deterred to use it in an investigation of sterility when it appears indicated.

CONCLUSIONS

1. Studies based on the result of the investigation of tubal patency in 706 consecutive cases are recorded. Two mortalities are reported.

2. The relative merits of carbon dioxide insufflation and lipiodol injection are considered. The view is expressed that carbon dioxide insufflation should always precede the use of lipiodol, as it gives all the necessary information in the majority of cases without some of the drawbacks of lipiodol. The use of lipiodol should be reserved in the main for those cases of nonpatency in which accurate localization of the obstruction is desired.

3. The therapeutic value of uterotubal insufflation is seen in many ways in cases of partial obstruction; a greater or more normal degree of patency may be established in certain cases showing a complete obstruction. Tubal patency may be re-established by the breaking down of adhesions, the expulsion of a plug of mucus or the straightening out of kinks. Dysmenorrhea is sometimes relieved; pregnancy follows insufflation in a certain proportion of cases.

4. My personal experience and the review of literature indicates that routine lipiodol injections are not harmless and that as a diagnostic method lipiodol injections carry a morbidity and mortality even though small. In sterility cases in which one tube is occluded, or both tubes show partial obstruction as demonstrated by air insufflation, lipiodol injection should be used cautiously, as complete occlusion may result and thus defeat the primary objective.

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THE INTRACERVICAL SURVIVAL OF SPERMATOZOA*

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IN THE analysis of sterile matings, it was formerly considered that the fertility of the male coincided very closely with the motility of the spermatozoa. Consequently motility tests were regarded as an integral part of fertility examinations. About twenty years ago intra-cervical postcoital examinations for spermatozoa and sperm motility were introduced by Huhner,¹ and these tests have since grown into rather general use in sterility investigations. Popularly such tests were regarded as a means of determining a compatibility between male and female secretions, and as a corollary to this the failure of conception became regarded in many cases as a result of incompatibility of secretions. Proof of such incompatibility of the secretions of normal males and females, in the sense that one type of normal blood is incompatible with another blood type, was not forthcoming. Neither was it clear to what extent negative findings indicated defective spermatozoa on the one hand or some disturbance of the female host on the other hand. Curiously enough, clinical analyses and evaluations of motility observations are notably absent from medical literature, possibly the result of the great difficulties encountered in taking into consideration the many variables, including personal equation, which affect motility observations.²

Between the years of 1920 and 1927 animal investigations revealed a definite relation between structural spermatie anomalies and reproductive fitness.³ These observations were later confirmed by various observers with both the lower animals and man, and it became generally recognized that a careful study of the morphologic characteristics of sperm populations furnished information about reproductive possibilities that no other tests had previously provided. The idea that

*The clinical material used in the preparation of this paper was derived in about equal proportions from the private cases of the two authors and from clinic cases from the Free Hospital for Women, Brookline, Mass.

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motility observations for estimation of fertility furnished per se a satisfactory criterion became no longer tenable. This brought up the question of relative significance of various tests applied to sperm populations.

Motility observations, if they are to be of clinical significance, must to some extent indicate the fitness of the spermatozoa for reproduction. The purpose of this paper is to present the motility observations on a group of sterile matings that have been extensively studied, in the hope that the clinical significance of motility may be better understood, particularly the motility which is observed on postcoital examinations. Such observations are often inconsistent with what might be clinically anticipated and seem to have little connection with either the seminal picture or the ability of the woman to conceive. One must admit that, if two fertile individuals mate normally, live spermatozoa should be found in the cervical canal at some period subsequent to coitus. Clinically, however, postcoital observations do not seem to bear out this rule, possibly due in many of the cases to a very brief survival period in the cervical canal or to an unsatisfactory means of securing specimens. Immediately subsequent to coitus the stronger spermatozoa should be able to migrate upwards past the cervical barrier and attain a position suitable for fertilization. The question then arises as to the most significant period for making a postcoital examination. If the examination is made too early, it may not measure the ability of the sperm to survive; if the examination is made too late, the test records either the ability to survive beyond any physiologic need for such survival or the death of the spermatozoa at a period when survival is not necessary or physiologic. The optimum time for making such examinations probably lies somewhere between two and fifteen hours after coitus, but it remains to be proved what lapse of time, if any, is optimum during this period. Spermatozoa in considerable numbers occasionally will be found in the cervical canal after forty-eight to seventy-two hours, but during this period the incidence of positive tests drops off so sharply that examinations are hardly worth attempting.

In cases of lack of motility or absence of spermatozoa in the cervical canal after normal intercourse, one is inclined to presume either that there is some abnormality of the spermatozoa or some alteration in the character of the secretions of the male or female tract. The former is most likely due to some somatic disorder, glandular or otherwise, which impairs the health of the spermatogenic tissue. The latter may conceivably result from a local disorder of the genital tract of either partner, some general disorder which affects the character of the genital secretions, or some introduced chemical factor such as contained in a lubricant.

If the clinical significance of the postcoital examinations is to be interpreted, it is highly desirable that the factors responsible for neg-

ative tests shall be better understood. Accordingly, we are here presenting observations on some of the somatic and germinal cell factors which presumably might influence, either directly or indirectly, the survival time of spermatozoa in the cervical canal, and we have attempted to correlate them with the postcoital determinations. These observations include:

- a. Period of menstrual cycle at which test was performed
- b. Spermatic pathology
- c. Somatic disease
 - (1) Systemic
 - (2) Pelvic (male and female)

We have excluded from consideration all cases in which no accurate record of menstrual dates were obtainable and all cases in which the ratio and type of spermatic anomalies have not been determined. Detailed physical examinations were made on all of the couples, and upon many an extensive laboratory work-up was done, including a determination of the basal metabolic rate, complete blood count, Wassermann test, examination of the prostatic secretion, and urinalysis. Endometrial biopsies and tubal insufflations were performed on most of the women. All males involved produced a sufficient number of motile cells that one might reasonably assume the possibility of these cells gaining entrance to the cervix. Further the history of the cases leaves little doubt that the seminal fluid was placed normally in the vagina in all cases. There were no structural or anatomic obstacles to insemination in either partner or history of faulty coital technique. Seventy-one couples of our series complied with these requirements. Out

TABLE I. RELATION OF PERIOD OF MENSTRUAL CYCLE TO SURVIVAL OF SPERMATOZA IN THE CERVICAL CANAL (TESTS MADE ON 71 STERILITY CASES)

PERIOD OF MENSTRUAL CYCLE	TOTAL TESTS	POSITIVE TESTS	NEGATIVE TESTS	PER CENT POSITIVE
4-9	18	10	8	55.5
10-12	26	8	18	30.8
13-15	31	15	16	51.7
16-18	33	17	16	51.5
19-21	23	8	13	34.8
22-24	19	8	11	42.0
25-28	25	9	16	36.0
	175	75-42.8%	100-57.2%	

In the construction of the array upon which Table I is based, due correction for menstrual cycles of different lengths was effected by means of charting the last fourteen days of all menstrual cycles so as to fall on the last fourteen days of the array, which is based on a theoretic normal of twenty-eight days. This caused the theoretic day of all ovulations to fall at approximately the same point in the array. Without this correction, the days of ovulation would have been too widely scattered in the array to permit any appreciation of a possible effect of cyclic ovarian changes, particularly that exerted by the maturation of the ovum.

of the 175 postcoital examinations of these cases, 75, or 42.8 per cent, were positive and 100, or 57.2 per cent, were negative. We have here arbitrarily considered a test as positive if one or more active spermatozoon per high power field is found in the intracervical mucus. A requirement of a larger number of active spermia naturally would somewhat reduce the ratio of positive postcoital tests. When a majority of postcoital tests are positive, we have considered the case itself as positive.

RELATION OF PERIOD OF THE MENSTRUAL CYCLE TO INTRACERVICAL SURVIVAL OF SPERMATOZOA

It is the common observation that at about midperiod (the expected period of ovulation) and for three or four days preceding there is an outpouring of clear glairy mucus from the cervical canal. Seguy⁴ and others regard this mucus as a particularly favorable environment for the

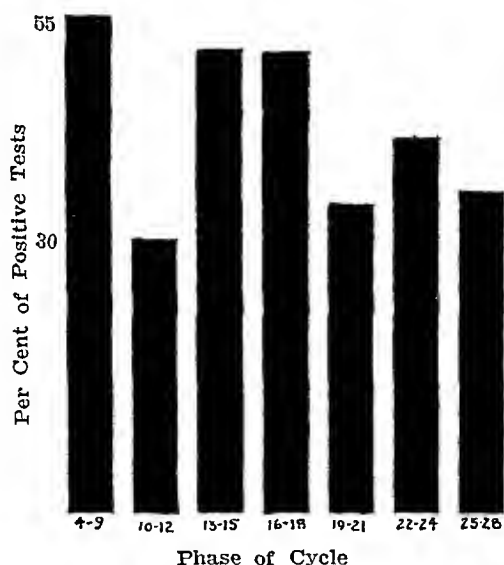


Chart 1.—Incidence of positive postcoital tests at various stages of the menstrual cycle.

migration of spermatozoa, and indeed to one who has made many postcoital examinations it is obvious that spermatozoa found in estrual mucus exhibit an agility of motion not commonly encountered in the thicker and more tenacious mucus of other periods of the menstrual cycle. Accordingly it was felt that the period of the menstrual cycle at which the test was performed might influence the results. The results of our tests have therefore been staggered according to the time of the cycle at which they were made (Table I).

Although statistically, the number of cases and the number of tests is insufficient, there does appear to be in the menstrual cycle a reduction in the ratio of positive tests from the tenth to the twelfth day inclusive and again from the nineteenth to twenty-eighth day inclusive, but this

effect certainly is not sufficiently marked to justify the conclusion that the cyclic changes of the female genital tract exert any striking influence on the ability of the spermatozoa to survive in the cervical canal (Table I, Chart 1). If however, the positive tests are treated as a group, we find that they form a monomodal curve with its apex between the thirteenth and eighteenth day of the cycle, whereas the negative post-coital tests are distributed somewhat more evenly throughout the course of the cycle. A positive test is more readily obtained if adequate mucus is present in the cervical canal, yet large numbers of highly motile spermatozoa are frequently found in the cervical canal at different periods of the menstrual cycle when cervical mucus is scant.

TABLE II. MAJORITY OF POSITIVE POSTCOITAL EXAMINATIONS
37 CASES

CASE	NO. OF TESTS		SPERM DENSITY*	PER CENT PATHOLOGIC SPERMIA	PER CENT INITIAL MOTILITY
	POS.	NEG.			
61	1	0	383.0	16.0	95
65	2	1	52.0	28.0	60
69	1	0	17.0	68.0	
78	1	0	128.0	18.0	75
79	1	1	25.0	21.0	50
90	1	0	52.0	41.0	
91	2	0	147.0	13.0	75
93	1	0	100.0	19.0	
95	2	0	60.0	32.0	60
96	4	2	79.0	25.0	10
97	1	0	143.0	17.0	
98	1	0	5.0	23.0	
101	2	0	95.0	10.0	75
103	1	0	178.0	15.0	75
107	1	1	84.0	22.0	75
109	1	1	219.0	32.0	75
115	1	0	84.0	28.0	80
118	2	0	111.0	12.0	90
122	1	0	90.0	69.0	None†
125	3	0	129.0	16.0	95
128	1	0	51.0	25.0	50
129	1	0	74.0	30.0	
131	1	0	122.0	22.0	20
138	1	0	198.0	21.0	
144	7	1	73.0	30.0	85
148	1	0	150.0	21.0	None†
151	1	0	23.0	57.0	30
153	1	1	155.0	77.0	15
155	2	1	22.0	14.0	15
162	2	0	49.0	26.0	35
169	1	1	48.0	14.0	90
177	3	1	148.0	13.0	95
184	3	3	98.0	28.0	60
185	1	1	12.0	20.0	95
187	1	1	139.0	15.0	70
188	4	0	113.0	14.0	50
195	1	1	16.5	27.5	95
Total	62	17			

*Millions per cubic centimeter.

†Condom sample improperly obtained for motility test.

Out of 71 sterile matings, 26 (36.8 per cent) gave only negative post-coital findings. Two of these individuals conceived. Forty-five cases (63.4 per cent) gave one or more positive tests. Nine of these individuals conceived, two of which received more than one test. Seven out of the 9 conceived before another test could be applied, thus furnishing insufficient data to indicate in themselves any ratio of positive and negative tests in fertile individuals. Two or more postcoital examinations were applied to 42 out of the 71 cases, and of these, 7 (16.5 per cent) were positive in all tests. On the other hand there were very few cases in the series that were persistently negative if three or more tests were applied

TABLE III. NEGATIVE POSTCOITAL EXAMINATIONS (26 CASES)

CASE	NO. OF TESTS		SPERM DENSITY*	PER CENT PATHOLOGIC SPERMIA	PER CENT INITIAL MOTILITY
	POS.	NEG.			
51	0	2	34.0	36.0	50
62	0	1	19.0	35.0	80
63	0	2	102.0	36.0	70
64	0	1	10.0	43.0	95
73	0	1	101.0	15.6	80
74	0	1	46.0	38.0	
81	0	6	26.0	20.0	20
84	0	2	22.0	24.0	10
85	0	1	10.0	22.0	40
99	0	3	253.0	25.0	85
108	0	1	123.0	19.0	
110	0	2	78.0	80.0	25
111	0	2	38.0	20.0	
112	0	2	69.0	62.5	None†
114	0	1	61.0	26.0	85
127	0	1	21.0	28.0	
130	0	3	7.5	15.0	
132	0	3	79.0	12.0	50
137	0	6	60.0	30.0	
140	0	1	9.0	100.0	
141	0	1	68.0	35.5	5
154	0	1	33.0	21.0	
167	0	1	303.0	21.0	85
175	0	2	92.0	22.0	95
194	0	2	288.0	17.0	
196	0	1	55.0	45.0	30
Total	0	50			

*Millions per cubic centimeter.

†Condom sample improperly obtained for motility test.

TABLE IV. MAJORITY OF NEGATIVE POSTCOITAL EXAMINATIONS (8 CASES)

CASE	NO. OF TESTS		SPERM DENSITY*	PER CENT PATHOLOGIC SPERMIA	PER CENT INITIAL MOTILITY
	POS.	NEG.			
67	3	4	28	31.0	50
72	1	7	28	51.0	50
75	1	2	101	20.0	80
124	1	3	132	14.0	
126	3	4	80	65.0	
135	2	8	101	38.0	60
143	1	2	63	38.0	20
181	1	3	141	15.5	
Total	13	33			

*Millions per cubic centimeter.

(5 out of 21). It seems that a little more persistence in repeating the tests should in most cases result in positive tests. It would therefore appear irrational to draw conclusions as to fertility on the basis of only one or two tests. It is possible, however, that the cumulative information of repeated postcoital examinations may have some clinical significance if the factors responsible for negative tests were recognized.

RELATION OF SPERMATIC PATHOLOGY TO INTRACERVICAL SURVIVAL

Cases with a high frequency of spermatic abnormalities occurred about twice as frequently among the group with predominantly negative postcoital examinations as among the positive postcoital cases (Table V).

TABLE V. RELATION OF INTRACERVICAL SPERM SURVIVAL TO SPERMATIC PATHOLOGY
A total of 79 tests were applied to the 37 positive cases and 96 tests to the 34 negative cases

	NUMBER OF CASES	CASES WITH OLIGOSPERMIA	CASES WITH SPERMATIC ANOMALIES 30 PER CENT OR MORE	TOTAL CASES WITH OLIGOSPERMIA AND PATHOLOGIC SPERM POPULATIONS
Positive postcoital cases	37	9 or 24.4%	9 or 24.4%	16 or 43.2%
Negative postcoital cases	34	14 or 41.1%	16 or 47.0%	23 or 67.8%
Total	71	23 or 32.4%	25 or 35.2%	39 or 55.0%

Further if we consider merely the incidence of negative tests per case, we find that these occurred at the rate of 1.70 per case with pathologic sperm populations in contrast to a rate of 1.00 per case in normal-appearing populations (Table VI). On the other hand, ratios are misleading in clinical interpretations since 8 out of 38 pathologic sperm populations produced only positive postcoital tests.

TABLE VI. RELATION OF NEGATIVE POSTCOITAL EXAMINATIONS TO NORMAL AND PATHOLOGIC SPERM POPULATIONS

	NO. OF CASES	TOTAL TESTS	NEGATIVE TESTS	PER CENT NEGATIVE TESTS	NEGATIVE TESTS PER CASE
Pathologic populations*	39	103	68	66.0	1.7
Normal sperm populations	32	72	32	44.5	1.0
Total	71	175	100		

*Sperm populations have been considered as pathologic either if they contained less than 50 million spermatozoa per cubic centimeter, or if the number of spermatic anomalies exceeded 30 per cent. Many of the cases with high ratios of spermatic anomalies presented also a diminished spermatogenesis, as indicated by an abnormally low count of spermatozoa per cubic centimeter.

It is quite evident that positive postcoital examinations furnish no satisfactory evidence of spermatic health, although it appears that a preponderance of negative tests occurred in about two-thirds of the cases with demonstrable spermatic disease.

RELATION OF IN VITRO MOTILITY TO INTRACERVICAL SPERM SURVIVAL

The degree of initial motility fails to provide a satisfactory index to intracervical sperm survival. The ratio of cases with a predominance of positive postcoital tests was 17.7 per cent greater with cases having a sperm motility of over 60 per cent than with those having less than 60 per cent. On the other hand, nearly half of the semen specimens with unsatisfactory in vitro motility gave a preponderance of positive postcoital tests (Table VII).

TABLE VII. RELATION OF IN VITRO MOTILITY TO INTRACERVICAL SURVIVAL

	NO. OF CASES	POSITIVE POSTCOITAL CASES	NEGATIVE POSTCOITAL CASES
Poor motility (motility less than 60%)	23	11 or 47.8%	12 or 52.5%
Good motility (motility more than 60%)	29	19 or 65.5%	10 or 34.5%
Total	52	30 or 57.7%	22 or 42.0%

We have made no attempt to correlate the type, degree, and duration of motility. On theoretical grounds it has long been recognized that variations in motility occur as the result of a vast variety of influences, such as temperature, time since ejaculation, condition of nutrition of the sperm, hydrogen ion concentration, and chemistry of the male and female secretions. Although such variations must necessarily jeopardize the value of motility tests for clinical purposes, it is evident that most motility tests are performed without regard to the physiochemical factors which, under normal conditions, may markedly influence motility. The question then arises as to whether motility variations are the result of pathology or merely represent incidental physiochemical variations. Our observations further indicate that reduced in vitro motility is about twice as frequent when pathologic sperm populations are concerned, but because of the observation that about 40 per cent of pathologic populations exhibit normal motility and about 30 per cent of normal populations show impaired motility, one is led to the conclusion that in vitro motility in itself is likely to be highly misleading.²

RELATION OF SOMATIC DISEASE TO INTRACERVICAL MOTILITY

An analysis of somatic disease of the male reveals no essential difference in the intracervical survival of spermatozoa between physically negative men and those having genital pathology. The number of cases with systemic disorders aside from hypothyroidism* is too small for any inference to be drawn. Of 11 hypothyroids, 8, or 72.7 per cent, produced positive postcoital tests.

*Cases were considered as hypothyroids if the basal metabolic rate was minus 10 per cent or lower, although they might be merely instances of low metabolic rates rather than true hypothyroidism. The eleven males whose rate fell below this figure averaged minus 19.9 per cent, while the average of thirteen hypothyroid females was minus 17 per cent.

The evidence of the influence of female somatic disease upon intracervical survival of spermatozoa is rather contradictory. Contrary to what is commonly supposed, 50 per cent of the cases with cervical pathology produced positive postcoital tests, in comparison to 48.0 per cent positives in the series of 71 cases as a whole. The tabulations revealed an apparent increase in the ratio of negative postcoital tests in the group of cases with anovulatory menses and in the group of cases with evidence of tubal disease or pelvic inflammatory disease. Inasmuch as the series contained no active cases of pelvic inflammatory disease, it seems unlikely that the pelvic pathology was instrumental in raising the ratio of negative postcoital tests. Physically negative cases gave a higher ratio of positive tests than the group as a whole (62.5 per cent positive). In the group of cases with a low basal metabolic rate, there was also an increase in the ratio of positive postcoital tests (69.0 per cent positive postcoital cases).

TABLE VIII. ANALYSIS OF MALE SOMATIC DISEASE

	NO. OF CASES	POSITIVE POSTCOITAL CASES	NEGATIVE POSTCOITAL CASES
Total cases	71	37 or 52.0%	34 or 48.0%
Physically negative	54	29 or 53.6%	25 or 45.4%
Genital pathology including testicular hypoplasia	12	5 or 41.7%	7 or 58.3%
Systemic disease	3	0	3 or 100%
Hypothyroidism	11	8 or 72.7%	3 or 27.3%

TABLE IX. ANALYSIS OF FEMALE SOMATIC DISEASE

	NO. OF CASES	POSITIVE POSTCOITAL CASES	NEGATIVE POSTCOITAL CASES
Total cases	71	37 or 52.0%	34 or 48.0%
Physically negative	32	20 or 62.5%	12 or 37.5%
Cervical disease endocervicitis, erosions, cysts, stenosis	22	11 or 50.0%	11 or 50.0%
Tubal disease and pelvic in- flammatory disease	19	7 or 36.8%	12 or 63.2%
Proliferative endometrium, genital hypoplasia	10	3 or 30.0%	7 or 70.0%
Systemic disease	4	2 or 50.0%	2 or 50.0%
Miscellaneous disorders; men- strual, tubal	10	5 or 50.0%	5 or 50.0%
Hypothyroidism	13	9 or 69.0%	4 or 31.0%

SUMMARY

We have here presented a correlation study of the effect of the more common somatic and germ plasm factors which might conceivably influence the intracervical survival of spermatozoa. These studies suggest that a variety of factors may influence intracervical survival, but that the effect is neither uniform nor sufficiently pronounced to permit an estimation of the degree of fertility, or to enable the use of such tests for the recognition of any given underlying etiologic factor.

An apparent increase in the ratio of positive tests occurred in the series of cases studied on the fourth to the ninth day of the menstrual cycle and again on the thirteenth to the nineteenth day. Analyzed from the viewpoint of either the male or female a low basal metabolic rate seemed markedly to improve intracervical survival. Women whose physical examination was entirely negative gave a little higher ratio of positive postcoital tests. A lessened intracervical survival occurred with:

- a. An increased incidence of pathologic spermatozoa. (9 out of 25 cases with high incidence of pathologic spermatozoa, or 36 per cent, gave positive postcoital tests.)
- b. Patients with anovulatory menstruation and genital hypoplasia. (30 per cent gave positive postcoital tests.)
- c. Pelvic inflammatory disease and tubal pathology including no active cases. (36.8 per cent gave positive postcoital tests.)

The occurrence of positive and negative postcoital tests appears for the most part to follow a pattern of chance distribution. The mere observation of motility and immotility is largely worthless and misleading. It is quite clear that tests of this nature are not highly pathognomonic of any given disorder and accordingly in themselves provide an exceedingly questionable means of appraising sterility.

METHODS AND TECHNIQUE

Postcoital Examination.—Tests for the presence of spermatozoa in the cervical canal are made within two to fifteen hours after coitus. Without the use of any antiseptic, the external os is thoroughly wiped off with a cotton pledget. Mucus is then removed from the cervical canal with a pair of long thumb forceps, transferred to a microscope slide and covered with a cover slip. It is then examined under a high dry lens and the number of cells and the ratio of motile cells per average high dry field recorded. Arbitrarily in this paper, we have classed as positive those tests in which the average field shows one or more active spermatozoa.

Some question must necessarily arise as to the best method of obtaining intracervical mucus and also as to what constitutes the best criterion of a so-called positive postcoital test. These factors appear to be based upon the opinions of various observers, and not upon statistical evidence. Therefore the question of the validity of methods and the criteria that are given here cannot well be answered until other methods and criteria have been analyzed. In the light of our rather negative results, such a study would be of value. Although the time after coitus and the number of spermatozoa found have been recorded in all of our 175 postcoital examinations, the group of observations is too small to permit a minute breakdown of figures on the basis of numbers of spermatozoa found, degree of motility, and number of hours postcoitus, without producing groups so small as to make the entire analysis valueless. Further, there seems to be no published study by which standards may be fixed or by which our arbitrary methods and standards may be checked.

Semen Examination.—a. Obtaining sample: Usually withdrawal specimen ejaculated directly into a wide-mouthed bottle or jar, transported to office within two or three hours, and kept at approximately room temperature until delivered.

- b. Record of amount and character of seminal fluid.

c. Density of spermia in ejaculate. Method: To 0.5 c.c. of semen in a graduated cylinder, a 0.5 per cent chloramine-T* solution is added to bring volume to 5 c.c., thus making a 1:10 dilution. Chloramine, by thinning the mucus, aids in effecting a more even distribution of the spermatozoa in the fluid. This suspension is transferred to the hemocytometer chamber with a dropper pipette, and five small squares are counted as in making a red blood count. The sum of the five squares is multiplied by 500 to obtain the number of spermatozoa per c. mm. or by 500,000 to obtain the number per c.c. If the count is less than 25,000 per c. mm., it is usually best to dilute the semen less or not at all and make a corresponding change in the calculations.

d. Motility in Vitro: Specimen kept at room temperature and observations made first within two or three hours after ejaculation and then once or twice daily until motility has ceased. Recordings are made with the fresh specimen in the following items:

1. Ratio of cells motile
2. Degree of motility
3. Duration of motility
4. Presence of pus or other extraneous cellular material in semen
5. Presence of cytoplasmic extrusions, free, and attached to spermia

For the purpose of this paper we are using only the initial ratio of motility.

e. Morphology of Spermia: All specimens were stained by one of Williams' staining methods,⁵ and the classification of sperm populations based on Williams' sperm classifications.^{6, 7}

We wish to express our appreciation to Dr. John Rock, Free Hospital for Women, Brookline, Mass., for many helpful suggestions and for the contribution of much clinical material used in the preparation of this paper.

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*Paratoluenesodium sulfonchloramide.

EFFECT OF PROGESTERONE ON UTERINE CONTRACTIONS

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IT WAS long suspected, before actual proof became available, that the corpus luteum was an inhibitor of uterine contractions. This suspicion arose from the observation that suppression of uterine contractions paralleled the life of the corpus luteum.¹ Since 1929 there has become available potent extracts of the corpus luteum, and more recently, the synthetic progesterone.² These discoveries were followed by a mass of animal experimentation. An exhaustive monograph describing the early changes in the uterus of the pregnant rabbit was published by Knaus.³ The livid, flaccid uterus associated with pregnancy and the development of the corpus luteum were graphically described. That this flaccidity was the result of corpus luteum influence and not the pregnancy directly was proved by experiments with sterile coitus in the rabbit. Sterile coitus was shown to induce follicle rupture and corpus luteum development which was followed by the same uterine relaxation as that seen in pregnancy. A number of investigators have confirmed this observation.⁴ This has been described as the reaction of pseudo-pregnancy.

By means of "in vivo" studies, using for the most part the artificially produced uteroabdominal fistula, the effect of corpus luteum extracts and synthetic progesterone have been studied.⁵ These observations have been made on the rabbit and confirmed directly or indirectly by experiments on the cat, cow, and sow. Experiments on excised uterine muscle have been unsatisfactory because of the insolubility of the hormone. There is abundant evidence which no one could deny that progesterone inhibits uterine contractions in certain animals.

Several years ago Falls published the results of certain experiments on the human being, using the aqueous extract of corpus luteum.⁶ An intrauterine balloon connected to a mercury "U" tube with a writing point on one arm was used to record the contractions on a kymograph. Inhibition of uterine contractions within an amazingly short time was recorded. I have not been able to confirm this work. In fact, I have not been able to demonstrate any inhibitory action of progesterone on uterine contractions. It was to be expected that such a report, however, would be enthusiastically received by the profession for the treatment of conditions wherein there appears to be a hypercontractility of the myometrium. The results of extensive animal experimentation and unconfirmed work on the human being inspired a premature conclusion

that progesterone would be indicated in the treatment of dysmenorrhea and threatened abortion. So widely accepted is this belief and so abundant the clinical reports that it seems well-nigh heresy to dispute it. However, the following experiments will speak for themselves.

SYNOPSIS OF THIS STUDY

A group of patients having a normal ovulatory menstrual cycle was selected for study. The pattern of motility during the follicular and corpus luteum phases was recorded before and after administration of progesterone. Uterine contractions in four cases of primary dysmenorrhea and one with threatened abortion have been studied before and after progesterone. Three patients in the puerperium were subjected to the experiment and their contractions recorded before and after progesterone.

TECHNICAL PROCEDURE*

A tenaculum was used to stabilize the cervix. After passing a small dilator through the internal os, it was possible to insert a small condom balloon attached to a flexible metal catheter into the uterine cavity. The cannula was connected to a rubber tube which led to a mechanical ink recorder, so situated that its writing point recorded the contractions of the uterus on a revolving kymograph equipped with a timer. The balloon and cannula were sterile. The balloon was then distended with sterile water until the pressure in the system was approximately 40 mm. of mercury.

To study the effect of progesterone on uterine contractions, a treatment schedule had to be established. After much consideration it was decided to give 15 mg. subcutaneously daily for four days, taking the tracing just before the first injection and about one hour after the last injection. In this way certain individual variations in response might be compensated for and the effect of the drug demonstrated whether the latent period of activity be short or long. In a few cases tracings were taken at other times during treatment; but since these were in all cases the same as those taken after completion of therapy, they are not reported. Unfortunately, we are in ignorance as to how progesterone is metabolized. Indeed, we do not even know how it is eliminated from the body; because it is possible to recover from the urine only traces of pregnanediol after large doses of progesterone.

EFFECT OF PROGESTERONE IN THE NORMAL CYCLE

The pattern of uterine motility in the normal ovulatory cycle is now well established. My observations confirm those of previous investigators in this respect.⁷ Uterine contractions during the follicular phase are characterized by low amplitude, high frequency, and considerable tonus. Several days following ovulation the contractions assume an

*The illustration of instrument for this procedure was published in this JOURNAL 42: 1024, 1941.

entirely new pattern. The amplitude of each contraction becomes higher, rate is markedly diminished, and the uterus becomes atonic as indicated by the contractions returning to a lower baseline (Fig. 1). This pattern of motility has been studied in a sufficient number of cases (18) to state unequivocally that it is the normal pattern of contractions in the ovulatory cycle. This shows that the effect of endogenous progesterone is one to inhibit the rate, increase the amplitude, and diminish tonus. The hypertonic uterus of the follicular phase is the result of unopposed estrogen influence. From this group of patients, four were selected to study the effect of injected synthetic progesterone. Two of them were treated as already described during the follicular phase, and two during the corpus luteum phase. Tracings are shown, one of which was taken just before treatment was started and the other about one hour after completing therapy. Examination of the tracings will reveal no change in the nature of the contractions either in the follicular or corpus luteum phase after the administration of progesterone (Fig. 1). No effect upon the rate, amplitude, or tonicity following 60 mg. of progesterone could be demonstrated.

NORMAL CYCLE

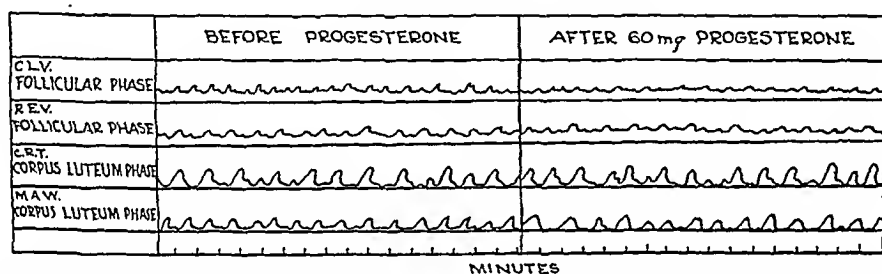


Fig. 1.—Normal cycle: Small amplitude, high frequency, hypertonic contractions during the follicular phase not altered by progesterone. High amplitude, low frequency, atonic contractions of the corpus luteum phase unaltered by progesterone.

EFFECT OF PROGESTERONE IN PRIMARY DYSMENORRHEA

Uterine contractions have been recorded in 15 patients with dysmenorrhea. The pattern of motility in the cycles of these patients was the same as in normal, nonpainful cycles except that the menstrual contractions are superimposed upon a hypertonic uterus. It can be seen from the tracings that the contractions of dysmenorrhea, taken while the patient was menstruating and experiencing her pain, do not return to the baseline because of the hypertonicity of the uterus. Contrast this with the atonic contractions during menstruation which will be described in a subsequent report. The tracings shown were taken on these four patients in two successive cycles. Tracings were first taken without any therapy; and the following month, taken on the same patient after 60 mg. of progesterone. Careful examination of the tracings (Fig. 2) fails to reveal any change in the rate, amplitude, or degree of tonicity. None of the patients reported any relief of pain following the 60 mg. of progesterone.

EFFECT OF PROGESTERONE ON THREATENED ABORTION

A young woman, aged 23 years, was seen in consultation when she was approximately three months pregnant. This was her first pregnancy. At the time of consultation she was hospitalized for pulmonary tubercu-

losis and was making satisfactory progress under collapse therapy. While the wisdom of therapeutic abortion was being considered by her physician, the patient began to have some vaginal bleeding. No attempt at treatment was instituted, because her physician felt that spontaneous abortion would be desirable. After several days of irregular bleeding, the patient began to have a few painful contractions. The cervix was

PRIMARY DYSMENORRHEA

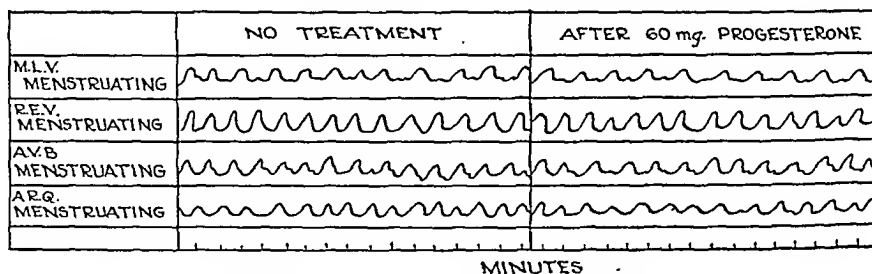


Fig. 2.—Primary dysmenorrhea: Tracings taken during menstruation, while patient was suffering her dysmenorrhea, were unchanged by progesterone.

THREATENED ABORTION

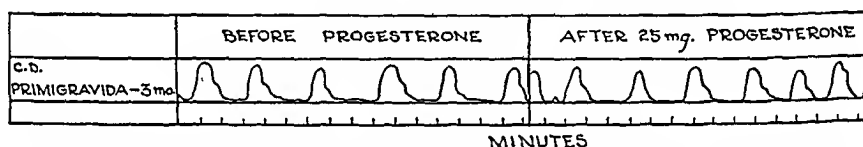


Fig. 3.—Threatened abortion: Uterine contractions recorded in a patient who was spontaneously aborting at three months were not affected by progesterone.

POST PARTUM

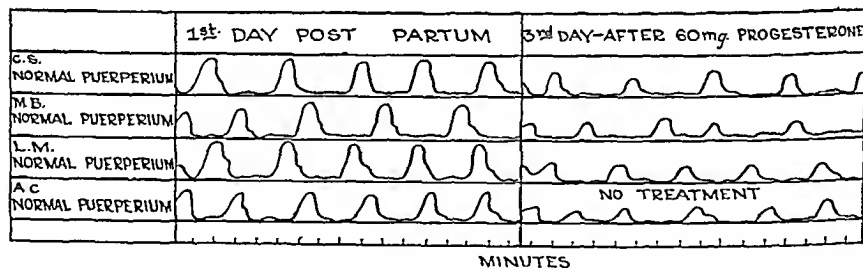


Fig. 4.—Puerperal contractions: The lower amplitude recorded after three days of progesterone therapy are physiologic and not the result of the hormone treatment.

one-finger dilated and abortion was thought to be inevitable. The balloon was passed into the uterus and the contractions recorded. The patient was then given 25 mg. of progesterone and the contractions were again recorded. No inhibition of the contractions could be demonstrated following the progesterone. The patient aborted about four hours after the balloon was removed (Fig. 3).

EFFECT OF PROGESTERONE ON THE POST-PARTUM UTERUS

Uterine contractions during the puerperium have been recorded in three patients following the administration of progesterone. Several clinical reports have described the relief of afterpains, using this hormone. None of these three patients had afterpains. They were all primiparas who had normal puerperiums. The first tracings were taken

on the first day post partum. Contractions occurred every four to six minutes and had a relatively high amplitude. Normally the contractions during the puerperium become progressively smaller, until after the twelfth day no intrinsic motility of the uterus can be demonstrated. This pattern of diminishing motility has now been observed in seven patients and will form the basis for a subsequent report. This normal sequence of events makes it difficult to evaluate the effect of a hormone when treatment extends over a period of three days. Nevertheless, three patients were given 60 mg. of progesterone during the first four days of the puerperium and tracings were recorded before and after the treatment. The contractions at the completion of therapy on the fourth day show less amplitude than they did before treatment, but this cannot be attributed to progesterone influence. The tracing on one control case, who received no treatment, is shown to indicate the normal amount of diminished motility which occurs. The diminished amplitude of contractions is a physiologic rather than a hormone effect (Fig. 4).

CONCLUSIONS

1. Uterine contractions before and after the administration of synthetic progesterone subcutaneously have been studied by means of an intrauterine balloon connected to a mechanical ink recorder which recorded the contractions of the uterus on a kymograph.

2. Synthetic progesterone has no effect upon uterine contractions in the normal ovulatory cycle, either during the follicular or the corpus luteum phase.

3. Synthetic progesterone has no effect upon the high amplitude, hypertonic contractions of primary dysmenorrhea.

4. Synthetic progesterone has no effect upon the uterine contractions in threatened abortion.

5. Synthetic progesterone has no effect upon the uterine contractions in the puerperium.

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THE EXTRAGENITAL EFFECTS OF DIETHYLSTILBESTROL

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REVIEW of the medical literature which has appeared since the introduction of diethylstilbestrol reveals a complete unanimity of opinion concerning the remarkable estrogenic effect of this and related chemical compounds. The evidence in this respect is entirely adequate, and stilbene drugs have universally proved to have a genital effect similar to that of the natural estrogens. To avoid further reduplication of data, therefore, this discussion concerns itself entirely with the extragenital effects of diethylstilbestrol. During the past year the patients in this Clinic who have received diethylstilbestrol have been studied for possible effects of the drug on systems of the body other than the reproductive tract.

MATERIAL AND DOSAGE

A total of 100 women are included in this report. The group includes only patients who could be observed long enough to be helpful in this study. They have been followed clinically for from two to twelve months and laboratory studies have been carried out at various intervals for as long as six months in some instances. All of the women had definite indication for the drug on the basis of clinical findings; no purely experimental patients are included. The doses used have been conservative, and in general have been based on the rule: Administer the minimum dose required to produce symptomatic relief. Specifically the dosage instructions for the average menopausal patient are these: 1 mg. a day for one week, then 1 mg. every other day for two weeks; starting with the fourth week, one tablet or capsule (1 mg.) as seldom as is compatible with freedom from symptoms. Such self reduction of dosage has resulted in a range from 1 mg. taken every two to three days to one patient who is afforded complete relief on 0.5 mg. taken every other week end. For cyclic therapy, 1 mg. daily for the first half of the menstrual cycle is usually sufficient. In children, 0.1 mg. twice a day for ten days will bring the vaginal pH down to 3.6 or 4.0. These dose ranges are in marked contrast to those reported in connection with the early "toxicity" studies of the drug and constitute, we believe, one of the factors responsible for the low incidence of unpleasant side effects in this study. These doses are, however, adequate to produce satisfactory therapeutic results.

GASTROINTESTINAL SYMPTOMS

From 93 of the patients, reliable histories were obtained concerning gastrointestinal symptoms. The average duration of therapy for this group was thirteen weeks, the average dose during this period was 44

mg. Eight patients, or 8.6 per cent, complained of nausea. Only two of these 8 actually vomited during the course of treatment. In 4 patients, the drug was discontinued. Two patients were "cured" by changing the type of tablet administered accompanied by reassurance. The nausea in all the remaining cases subsided with reduction of dosage. An additional 11 patients complained of epigastric distress, but these were inconstant, temporary, and often associated with unusual dietary history. These all subsided without discontinuation of therapy.

Nausea is the most frequently mentioned reaction in the diethylstilbestrol literature. Morrell¹ has recently reviewed this subject and found gastrointestinal symptoms reported in from 0 to 80 per cent of patients. The present report is not comparable to most of these series because of the difference in average dosage. While we used two forms of the drug (enteric coated and gelatin capsules), the incidence of nausea in our series was too small to permit of adequate comparison. Most of the patients took the medication at bedtime, often with a glass of milk. We feel that the effect of this compound on the gastrointestinal tract is minimal, and is entirely comparable with that encountered in other forms of chemotherapy.

LIVER FUNCTION

While none of the available liver function tests is completely satisfactory, the bromsulphalein test was felt to be as adequate as any for this study. Liver function studies were done on 53 patients and 107 bromsulphalein tests were carried out on these patients. A test was run on each patient before medication and again after treatment. The average time between tests was eight weeks, and the average dosage of diethylstilbestrol was slightly less than $\frac{2}{3}$ mg. per day. The half hour serum retention of bromsulphalein was determined and any retention above 10 per cent was considered abnormal rather than 15 per cent which is usually considered abnormal. Only 7 abnormal readings were encountered, and 5 of these occurred prior to administration of diethylstilbestrol. In two patients, 15 per cent retention of the dye was found after therapy but in each of these there was greater retention before treatment was instituted. In one of these the test was repeated again after an additional five weeks of medication, and there was only 5 per cent retention of dye. It is our opinion, therefore, that diethylstilbestrol in therapeutic doses has no effect on liver function demonstrable by this test. Other tests have been used,²⁻⁷ and as yet no clear-cut evidence has been found of any hepatotoxic effect of diethylstilbestrol.

BODY WEIGHT

Because the retention of water has been said to occur after administration of the estrogens, the weights obtained on the patients at the time of the bromsulphalein tests were compared. Considerable caution must be exercised in evaluating this figure, since many patients were simultaneously put on a general regimen which often included changes in diet. Furthermore, the majority of the postmenopausal patients reported a marked improvement in the sense of general well being and in appetite. The maximum gain (9 pounds in ten weeks) occurred in such a patient, and a total average weight change in the entire group during treatment (an increase of 0.149 pounds) is probably not significant as an index of fluid imbalance. So far as can be told from

this series, it can be said that diethylstilbestrol showed no tendency to produce any marked water retention.

RENAL SYSTEM

Urinary sediments were examined microscopically in 42 of the above group of patients before and after treatment. No patient had any demonstrable change in the constituents of the urinary sediment following therapy. One patient showed a trace of albumin both before and after diethylstilbestrol; no other patient showed albuminuria. In other words no deleterious effects on the renal system are reflected in the urinary studies. Other renal function and urinary studies which have been performed^{3, 6, 7} agree with this observation.

HEMATOPOIETIC SYSTEM

Eighty patients had complete blood studies before and after taking diethylstilbestrol. More than two-thirds of this group were menopausal patients; the average duration of therapy between laboratory studies was almost three months; the average total dose for this period was 46 mg. A total of 171 blood counts were performed.

The hemoglobin, red cell and white cell counts showed no significant or consistent changes. The average of each of these was slightly lower after therapy than before. This was within the limits of technical accuracy, but may be a reflection of the increase in blood volume which is said to occur with the administration of estrogenic substances.

One interesting observation which was made with respect to these blood constituents concerned the color index. Of the patients under 40 years of age, the color index showed an increase in only 27 per cent of the cases. Among the patients over 40, largely the menopausal group, the color index showed a rise in 64 per cent of the cases. This would tend to confirm the suggestion made by Hill⁸ that a low color index is an integral part of the menopausal syndrome and can be corrected by endocrine therapy. Other references in the literature to this change cannot be found, but it is possible to calculate from the data presented by von Haam and his associates⁶ that all 6 of their patients on whom blood studies were done showed an increase in the color index following the administration of diethylstilbestrol. Davis⁹ also states without commenting on the color index, that "in a small group of women with marked anemias of long standing, surprising improvement occurred after short intervals of diethylstilbestrol therapy."

Complete differential counts were performed on our group of patients. There were no marked shifts of white cell distribution or platelet count. The two most consistent and interesting findings were in respect to the monocytes and the eosinophiles. The monocyte count showed a rise of 2.7 per cent in 60 per cent of the patients. This relatively minor change occurred with sufficient frequency to impress us. The eosinophiles also showed a minor but definite increase. Disregarding any change of only 1 per cent, 35 per cent of the patients showed an increase of eosinophile count of about 3 per cent, on occasions rising as high as 8 per cent. There was no relationship between the occurrence of this mild eosinophilia and the gastrointestinal symptoms. In the cases where it was possible to follow the patients, this change had disappeared within two weeks after discontinuing the drug which is approximately the time required for reappearance of the menopausal symptoms. We

have no explanation for this mild and temporary eosinophilia, but feel certain that it is connected in no way with any so-called toxic reactions.

SUMMARY

During the past year, 100 patients receiving diethylstilbestrol for therapeutic reasons have been carefully observed and studied. All tests were controlled by performing them both before and after treatment. The observations reported relate to the effects of this drug on systems other than the reproductive organs. In general these extragenital effects duplicate those that have been found with the natural estrogens, and while many of these observations are of interest and invite further study, none of them can in any way be considered as representing toxic manifestations of diethylstilbestrol.

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THE CAUSES AND TREATMENT OF SECONDARY DYSPAREUNIA

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AS DEFINED by the various medical dictionaries, the term "dyspareunia" is derived from the Greek word, meaning "badly mated," and indicates difficult or painful coitus. Unfortunately it is that the psychiatrist, the psychosomatist, the psychologist, the gynecologist and the sociologist has each interpreted the term according to his own limited specialty. This terminologic discordance has done much to retard the clinical study of the subject of dyspareunia, relegating it to the files of minor problems. Certainly no symptom which can so easily and completely derange the emotional, marital, and physiologic normalcy of the patient can be considered of minor concern. Notwith-

standing the paucity of articles in the literature, the perfunctory paragraphs in most of the textbooks, and the apathy of the medical profession, the symptom of dyspareunia is of major importance to the woman so afflicted. The present-day confusion is directly referable to two factors: First, Kisch's interpretation of dyspareunia as an "absence of voluptuous sensations," and second, the pernicious practice of adding new terms, new definitions, and new interpretations without particular reason.

Common usage has established dyspareunia as meaning the association of pain with coitus, and it is so interpreted in this article. We have appended the term secondary to designate the type in which demonstrable pathology constitutes the underlying cause of the symptom. We appreciate that dyspareunia can and does occur in the absence of indubitable pathology, and to this group of cases the term primary dyspareunia is applicable. That primary dyspareunia can be entirely psychical in origin cannot be denied, but it is our opinion that a thorough investigation will, in the majority of instances, reveal the presence of secondary somatic factors. The oft repeated statement that physical causes cannot be established in over 50 per cent of otherwise normal individuals is not in agreement with our experience.

Dickinson aptly stated the basis for the difficulty in correctly presenting a statistical study of the subject, when he said that "the surgeon thinks of difficult coitus in terms of a knife passed through the muscles in spasm; the psychiatrist thinks of dyspareunia as a mental knot to be disentangled by analysis; the gynecologist who is tired of patching, poor and late patching, begins to think in terms of prevention through routine premarital examination and instruction." Our own concepts may be influenced by the fact that our material is basically gynepathic.

The almost universal tendency to disregard or to minimize the complaint of dyspareunia reflects the hesitancy of the profession to view realistically subjects which are not well understood. The allegation that the patient is affronted by queries as to her sex life is not well grounded. Rare is the patient who hesitates to answer questions regarding her welfare, when these questions are carefully worded and intelligently presented. The claim that the complaint of dyspareunia is infrequent is an admission that the subject has been entirely disregarded in the taking of histories. The old adage, "seek and ye shall find," is especially applicable to this complaint. Many of the patients endure the discomfort or actual pain for years, finally presenting themselves with an array of symptoms, so disconnected and bizarre, that the separation of the fact from the fancy strains the diagnostic acuity of the investigator. It is difficult to evaluate the signs and symptoms ascribable to dyspareunia, as they are so often beclouded by psychic and physiologic factors. The major part played by dyspareunia in cases of long stand-

ing may be completely "blacked-out" by the multiplicity of secondary complaints. Uniformly good results can be attained in the treatment of these symptoms only through a comprehensive attempt to uncover the cause or causes. It must be admitted that the removal or correction of the causes will not necessarily be followed by success in therapy. In the background of all of these cases there is probably a psychic factor, the importance of which is unpredictable. That gastrointestinal and pelvic symptoms, frequently resulting in unnecessary medical and surgical procedures, are serious sequelae, is a lamentable fact, explained by our almost complete disregard of the important relationship of the emotional and the physiologic activities of the body.

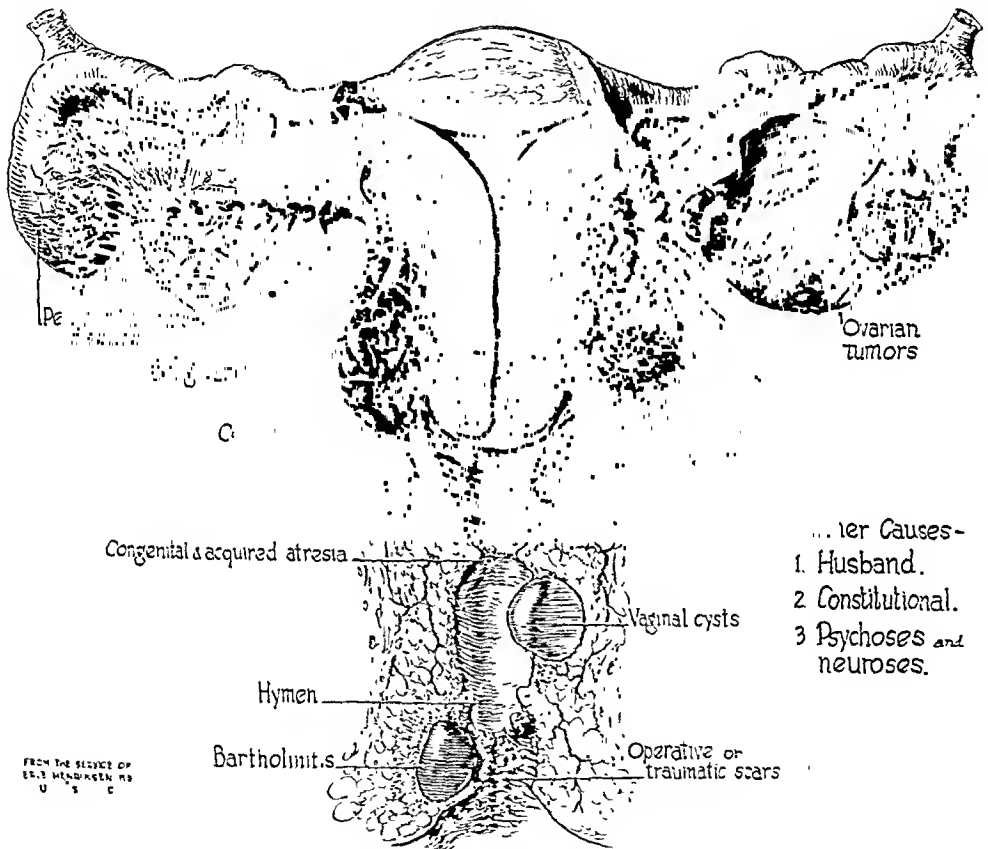


Fig. 1.—Causes of secondary dyspareunia.

The material herein presented represents a cross section of the so-called sociologic levels, with no attempt to index them according to social status. Though miscellaneous social and environmental factors appear more frequent in certain groups, the overlapping of factors is so multiple as not to permit satisfactory classification. Grouping by age is also impractical. However, for clarity and convenience, our material has been arranged according to major factors, conceding that a sharp segregation of the strictly pathologic from the truly psychogenic is impossible.

In Figs. 1 and 2 the demonstrable factors encountered in this study have been diagrammatically presented. The more common causes will fall into either the anatomic, the inflammatory, the neoplastic, the surgical, or the miscellaneous group, and no attempt will be made to discuss all of the factors.

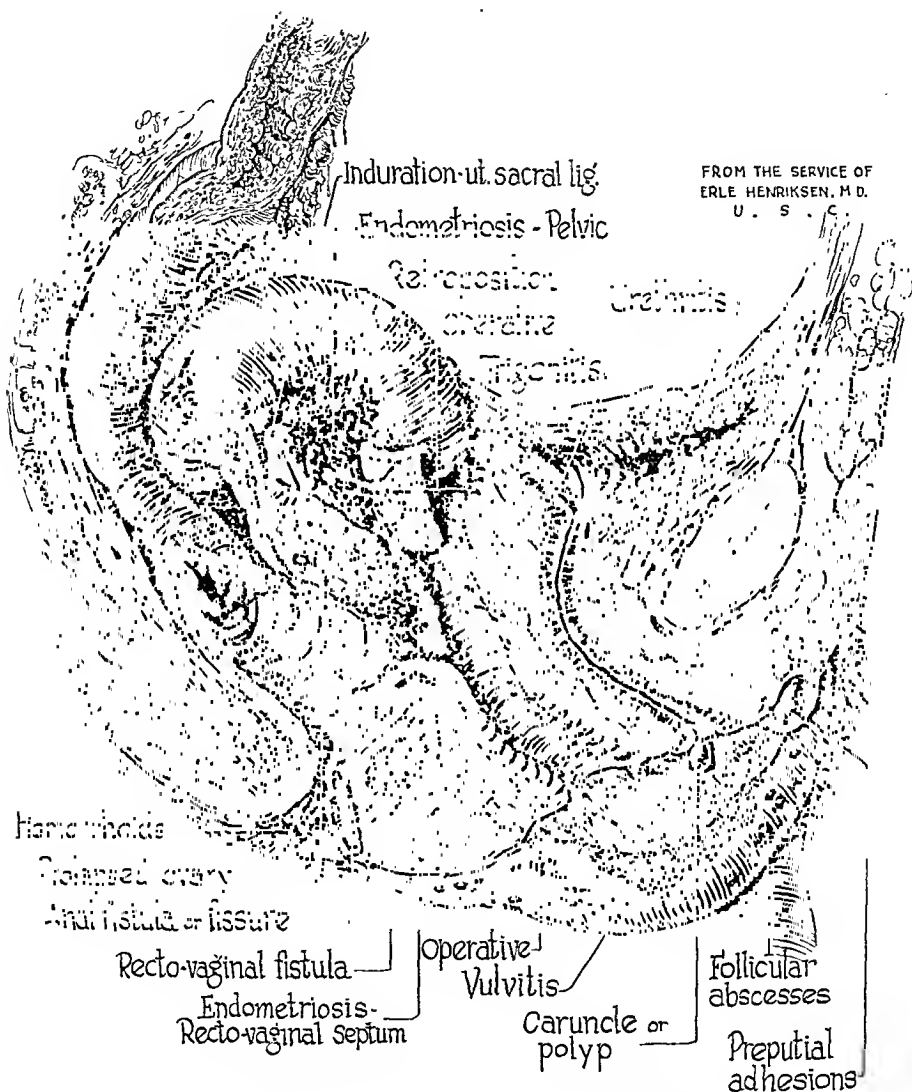


Fig. 2.—Causes of secondary dyspareunia.

ANATOMIC GROUP

1. Malposition of the urethral meatus exposing it to coital trauma must be treated by instruction in coital postural technique.

2. Congenital vaginal septa, vaginal bands and scars, and rigid unelastic hymens require graduated dilatations with or without plastic surgical procedures. The routine incision or excision of the hymen is frowned upon and should be replaced by careful premarital examination and adequate instruction. Some patients trace the onset of sexual difficulties to the premarital surgical incision of the hymen.

3. Absence of the vagina, though not a cause of dyspareunia, deserves mention because of its importance to the welfare of the patient. The success of plastic operations necessary to construct a functional vagina is dependent on two factors: First, the judicious selection of the surgical procedure best adapted to the individual, bearing in mind that there is no routine procedure in this type of surgery. Second, the careful evaluation of the social, environmental, and psychical factors so frequently disregarded by the surgical enthusiast.

4. "Married Virgins." In this group we place those pathetic women, who, notwithstanding years of married life, still have an unpenetrated hymen. It is this group that best demonstrates the need of proper premarital instruction and examination. The always present psychogenic disturbances make the successful treatment of these cases most unsatisfactory. Simple excision of the thickened hymen, belated instructions, and proper dilatation of the introitus must be accompanied with adequate psychotherapy. Complete cures, in this type of case, are infrequent, regardless of the thoroughness of the therapy.

5. Anatomie disproportion of the genital apparatus is surprisingly uncommon. These cases usually respond to complete explanation of the problem in the presence of both partners. Graduated dilatation and/or surgical procedures to enlarge the introitus may be indicated in the occasional instance.

INFLAMMATORY GROUP

1. *Vulva*.—Dermatologic diseases of the vulva manifest the same characteristics as they do in other portions of the body. These skin lesions may be so located as to cause dyspareunia and those of long standing may result in an incapacitating atresia of the introitus. The cure will be effected by appropriate treatment of the skin lesions. Skin changes appearing in the senium, viz., the various forms of leucoplakia-like lesions, may also cause atretic changes in the vaginal introitus. Though some skin lesions of the postmenopausal type may frequently respond to hormonal therapy, the true leucoplakic lesions usually require a surgical removal of the affected parts. A correctly performed radical vulvectomy should leave a physiologically adequate introitus.

Mention may be made of the gland of Bartholin in order to stress at least one point in the treatment of Bartholinitis. We permit several exacerbations of the involved gland before resorting to surgical incision, since it is our experience that many of these infected glands will subside completely following adequate drainage. The excision of the gland from the mucosal side may result in a painful scar.

2. *The Urethra*.—The presence of an urethral polyp or caruncle does not predicate their importance as a cause of dyspareunia. A careful digital examination of the urethra, especially of the posterior portion, is of much importance. The chronically indurated posterior urethra responds readily to careful dilatations of the urethra, followed by the topical application of an appropriate antiseptic. The indiscriminate destruction of the paraurethral ducts with the actual cautery may result in painful periurethral abscesses. Better results can be obtained in some instances by first stripping the paraurethral ducts over an urethral sound, followed by a thorough lavage of the duct. For this latter procedure a lacrimal duct needle is indispensable.

3. *The Ureter.*—Dyspareunia is commonly associated with pathologic changes in the ureter, be they inflammatory or structural in origin. The patient usually complains of bladder disturbances appearing at variable intervals following the sex act. One of our patients stated that she experienced severe dysuria, with increased urinary frequency, eighteen to twenty-four hours after coitus. The routine attempt to palpate the pelvic ureters is a valuable adjunct in gynecologic examination which is frequently disregarded. Routine cystoscopy and ureteral studies, however, are not indicated in the study of dyspareunia.

4. *The Vagina.*—Vaginitis, as a cause of dyspareunia, has become more common within the past decade. The increasing recognition of vaginal irritations associated with the presence of trichomonas vaginalis and the various species of the monilia type of fungi has been amazing. It is unfortunate for these patients that there is no universal form of therapy. It is our impression that other causative factors besides the trichomonads must be found before we fully understand how to treat this form of vaginitis. A carefully followed regime of diet, rest, personal hygiene, and exercise may often give relief when the advocated trichomonadocides fail.

Vaginitis secondary to a pathologic cervix or associated with the regressive and inflammatory changes of the senium readily responds to appropriate treatment. Traumatic lesions following improperly fitted contraceptive devices or supportive pessaries also occur, as do changes in the mucosa following the use of irritating chemical contraceptives or douches. We have been impressed with the many cases of so-called nonspecific lesions of the vagina that clear up following the withdrawal of all forms of therapy.

5. *The Cervix.*—Because of the poor nerve supply, lesions of the cervix are seldom the direct cause of dyspareunia. However, the supravaginal portion of the cervix is intimately connected with the base of the bladder and the lymphatic drainage from an infected cervix frequently produces the so-called aseptic and painful cystitis, with its syndrome of symptoms. The involved cervical lymphatics passing through the broad ligaments and along the uterosacral ligaments can account for the type of dyspareunia associated with deep penetration. Adequate dilatation of the cervical canal with proper cauterization is often followed by complete relief. Apparently there is no direct relation between the degree of visible cervical involvement and the amount of discomfort experienced by the patient.

6. *The Parametrium.*—Though a parametritis, secondary to gonorrheal infection of the cervix, is common, the importance of the post-abortual type of infection must also be considered. Cauterization of the cervix is interdicted under such conditions and conservative therapy offers the best results. The role of inflammatory lesions of the pelvic adnexa is difficult to evaluate. The acute processes are always associated with dyspareunia. The amount of discomfort in the chronic cases is usually dependent upon the degree of fixation of the pelvic structures. However, it is not uncommon to find minimal pelvic inflammatory lesions producing incapacitating symptoms, and it is in these cases that other factors, such as a low threshold of pain or psychic reactions, must be searched for. Thus the degree of tissue involvement does not necessarily predicate the severity of the symptoms.

NEOPLASTIC GROUP

Tumors of the vulva or vagina are relatively infrequent, except during the senile epoch. Hypertrophic granulomatous lesions may require radical surgical procedures, though in some instances the tissue destruction and the landmark distortion rule out any attempt at reconstruction. In several of our cases the vaginal vault has been entirely occluded by condylomatous growths of a benign character.

Tumors of the uterus are seldom associated with dyspareunia unless an intraligamentous nodule fixes the pelvic floor or a nodule becomes impacted in the cul-de-sac. Tumor masses large enough to distort pelvic landmarks may push the ovaries into the cul-de-sac where they are subjected to coital trauma. Mechanical obstruction by the tumor on the vascular bed of the pelvis may result in a painful chronic pelvic congestion or pelvic variecosities. The latter may occur in otherwise normal pelves and is not uncommon, especially in young women, who are on their feet all day.

The importance of cystic and solid tumors of the ovary depends on, first, their location in relation to the vaginal fornices and, second, the presence of adhesions between the tumor mass and the parietal peritoneum.

Pelvic endometriosis is one of the common causes of dyspareunia. A helpful differential point of diagnostic importance is that the pain is only affected by deep penetration and tends to radiate to the sacral area and down the legs. This syndrome is also common in the presence of indurated uterosacral ligaments secondary to an infected cervix. Endometriosis of the rectovaginal septum, the peritoneal surfaces of the cul-de-sac, the ovaries, and the uterosacral ligaments tends to produce irritating scars with resultant painful adhesions. Treatment is dependent upon the severity of the symptoms, the age of the patient, and the location and degree of tissue involvement. The routine employment of roentgen ray or surgical castration by tissue ablation is not considered a judicious procedure.

SURGICAL GROUP

This is by far the largest group and the underlying factors are legion. Paradoxically, a relaxed vaginal introitus may be the cause of a dyspareunia as severe as that experienced with an introitus that is too small. The discomfort in the presence of vaginal relaxation usually arises from a displacement of the pelvic structures, exposing the bladder to mechanical trauma. Why many surgeons give no thought to the sexual life of women in the third phase of life is difficult to understand and reflects a total lack of interest in the normal physiologic activities of the woman. This thoughtlessness is the cause of much unhappiness, both mentally and physically.

The most serious surgical transgression in the performance of plastic procedures on the vulva and vagina is the wholly unjustifiable one of some operators to apply certain routine operations to all patients. This will inevitably result in many failures, regardless of what may be the perfect technique of the surgeon. No single plan of surgery has yet been devised which is equally applicable to all cases.

Because of their basic importance, certain points in the operative technique for the correction of vaginal and pelvic floor relaxations de-

serve reiteration. The unanatomic practice of trying to approximate the levator muscles in the midline, by placing the sutures too deeply, is commonly accompanied by a thick painful transverse band of scar tissue. A more desirable method is the restoration of the levator relationship by the proper approximation of the levator fascia. This technique achieves adequate support with minimal scar formation. Of equal importance is the selection of suture material, realizing that a correctly performed operation does not require the heavy sutures so commonly used in the past. The indiscriminate sacrifice of tissue results in an inelastic vaginal introitus that may interdict normal sex life. The tendency of many to suture the orifice too snugly intimates an inferiority complex on the operator's part. The successful repair of the vaginal introitus is judged not alone by its cosmetic appearance, but by whether or not a physiologic norm is obtained.

At the present there is a rapidly growing wave of therapeutic enthusiasm for routine immediate post-partum repair of the cervix, the perineum, and whatever other portion of the birth canal is exposed sufficiently for the introduction of a suture. It is true that there are specific indications for the immediate repair of birth canal injuries, but routine "trimming and suturing" should be discouraged. Such plastic procedures demand a training usually limited to the specialist and are not for the occasional operator. This widespread application of the repair can be traced to the numerous reports tending to simplify the technique. Many of the authors forget that what seems a simple and safe procedure in their hands is fraught with danger in the hands of the inexperienced. The second criticism of many of these reports is their almost blatant disregard of a critical follow-up of the patients. Another unfortunate practice in obstetrics is the tendency to consider episiotomy as a procedure that should be routinely employed. Our study reveals that even in the hands of the experienced, the episiotomy may have painful sequelae, and dyspareunia is surprisingly common. The point of tenderness in these cases tends to localize just within the hymenal ridge. The treatment of these complications is not a resort to better postnatal surgical methods, but a full appreciation of the fallacy of advocating routine procedures regardless of indications. When a routine procedure is advocated, the advocate admits, in most instances, that he has lost the art of adaption.

The Cervix.—A too radical amputation or repair of the portio vaginalis of the cervix, with the resultant extension of the scars into the vaginal fornices, is commonly associated with dyspareunia. The pendulum is now on its return swing, and once more many clinics are advocating routine panhysterectomy, because of the danger of the subsequent development of cancer. It is true that the panhysterectomy removes the potential danger of malignant changes in the cervical stump, but the exceedingly low incidence of primary stump cancer casts doubt on the validity of this syllogism. The careful preoperative examination and treatment of the cervix will do much to lower the incidence of cancer of the stump. In a series of 37 women, seen ten or more years following total hysterectomy for uncomplicated myomatous changes in the uterus, 32 women complained of dyspareunia. Twenty-three of the patients stated that the discomfort was so marked as to make the sex act impossible. Careful examination disclosed shortened and immobilized vaginas, narrowing and scarring of the vaginal vaults, and/or senile

changes of the vaginal mucosa. In the hands of the experienced pelvic surgeon, the uncomplicated total hysterectomy does not shorten the vaginal vault, but the actual measurements of the vaginal vault of patients operated upon by many different surgeons, revealed an average shortening of 2 cm. Of 41 women, studied ten years or more following supravaginal hysterectomy for uncomplicated tumors of the uterus, only 13 complained of dyspareunia. Total hysterectomy does have its important place, but this procedure should not become a routine, and the cases should be selected.

The Corpus.—The inept selection of the proper surgical procedure for suspension of the uterus may terminate in a syndrome of symptoms more serious than those complaints for which the surgery is performed. Here again, the pernicious attempt to apply a single plan of surgery to all types of cases inevitably ends in many bad results. Pertinent observations in the treatment of uterine malpositions are, first, that the uterus in retroposition is not necessarily the cause of the patient's complaints, even though the presence of a pessary has brought relief. Second, an enlarged corpus with evidence of chronic congestion may cause more disturbance to the pelvic floor when brought forward than when it lay in the cul-de-sac of Douglas. It is not rare to see patients who date the onset of many complaints from a surgical suspension of the uterus for the attempted relief of multiple pelvic symptoms. Retroposition of the uterus, per se, rarely causes dyspareunia. Fortunately the operation for the correction of malpositions of the uterus is taking its proper place with the once favorite operation of suspending the kidneys.

MISCELLANEOUS GROUP

Fissures and fistulae-in-ano, hemorrhoids, and perirectal abscesses, though not often considered as possible factors in the cause of dyspareunia, have been found in several cases. Into the miscellaneous group must also be placed the individual in whom nothing can be demonstrated by digital examination and, in many instances, surgical exploration. These patients complain of pelvic discomfort and actual pain can be elicited by pressure on the cervix, the broad ligaments and the uterosacral ligaments. We have applied the term "pelvic causalgia" to this group and in a limited number have seen complete relief with resection of the superior hypogastric plexus. However, we do not of course advocate this procedure as a routine form of therapy.

Rare is the woman who will admit that her partner is responsible for her dyspareunia, though it is true that it takes two to produce the symptom. Though carelessness, awkwardness, and other such faults on the part of the male are frequent factors, the patients almost routinely deny their importance.

CONCLUSIONS

From the gynecologic standpoint the largest percentage of cases follow surgical procedures. A review of the various causes brings out the striking fact that a tendency to apply routine methods, with little attention to the physiologic importance of the parts involved, is the outstanding cause. Surgical enthusiasm should be tempered by careful and intelligent evaluation of each case and not by the stubborn desire of the operator to cling to one surgical procedure. Though we agree

with Dickinson that premarital examination and instruction are of great importance, we feel that better end results can be obtained by a widespread education of the medical profession.

Hidden away in every case are intangible factors such as fatigue, social and environmental disturbances, and general constitutional manifestations that can be brought to light only through intelligent study by the physician. Throughout this group of cases, regardless of the underlying pathology, runs a psychic current, so variable that without adequate psychiatric study its true importance cannot be evaluated. Though the demonstrable pathology or the structural defect can be removed or corrected, of equal import is the ability of the patient to readjust herself. The realization that a physical examination is of limited value without an attempt to determine the absence or the presence of the intangible factors will do much to minimize the medical and surgical failures. In all instances the personality of the patient should be studied. It is admitted that the various specialties tend to limit their diagnostic interpretations and therapeutic procedures within the scope of their own field, and this applies likewise to the treatment of dyspareunia. However, even with an admitted bias, we feel that the majority of these cases reveal definite pathology or structural defects, as the original basis of the complaint.

The treatment of dyspareunia is dependent on the identification of the causes and the removal or correction of these causes, be they physical or psychic in origin. To arrive at the correct interpretation presupposes thorough study of the personality, the environment, the severity and duration of the symptoms, as well as the patient's attitude toward both the complaint and her husband.

SUMMARY

1. The confusion in the study of dyspareunia results directly from a terminologic discordancy and the widespread apathy of the medical profession toward this problem.

2. The causes of secondary dyspareunia are grouped according to the major underlying factors, into anatomic, inflammatory, neoplastic, surgical, and miscellaneous groups.

3. The correct treatment is dependent upon the identification of the underlying cause and the proper evaluation of the so-called intangible factors.

4. Though pathologic changes or structural defects can be demonstrated in most instances, full cognizance must be taken of the psychic factor.

5. The importance of prevention therapy is overlooked. Not only are premarital examination and instruction valuable, but a fuller ap-

preciation by the physician of the need of a discriminatory selection of types of treatment is sorely needed.

6. From the gynecologic point, the most frequent single cause of dyspareunia is the attempt to apply routine surgical methods without individualizing indications.

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523 WEST SIXTH STREET

INFECTIOUS LESIONS ABOUT THE EXTERNAL GENITALS*

WITH SPECIAL EMPHASIS UPON THE DIAGNOSIS

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INFECTIOUS lesions about the external genitals of the female offer a particularly intriguing problem, since the same etiologic factor may produce variable lesions, and different etiologic factors may produce similar lesions. Several infections likewise may coexist. A close similarity in nomenclature helps further to becloud an already confused situation.

INCIDENCE

Because the admission of patients with vulvar infections to the gynecologic and dermatologic services of Bellevue Hospital is left entirely to the discretion of the admitting physician, the incidence of the various diseases is considered for each department individually (Table I). While the general incidence of syphilis on the gynecologic service is 4.7 per cent, patients with primary lesions about the external genitals have been observed in 1.4 per 1,000 admissions, and secondary lesions about the genitals in 0.9 per 1,000 admissions. The incidence of this latter condition is admittedly small because most patients with obvious secondary syphilis are admitted to the dermatologic service. Tertiary lesions have not been observed during the last five years. The apparently high incidence of lymphogranuloma has been somewhat surprising, with 5.2 per thousand admissions. Grace¹ reports an apparent in-

*Read, by invitation, at a meeting of the New York Obstetrical Society on December, 9, 1941.

crease of this disease in this locality. Granuloma inguinale has been observed in 0.4 per 1,000 admissions, chancroids in 0.8, condylomata acuminata in 2, and Bartholin abscess in 30.6 per 1,000 admitted patients.

TABLE I. INCIDENCE OF DISEASE, BELLEVUE HOSPITAL SERIES

GYNECOLOGY		DERMATOLOGY—FEMALES
Black admissions 41.9%		Black admissions 62.3%
White admissions 58.1%		White admissions 37.7%
General incidence of syphilis 4.7%		General incidence of syphilis 48.0%
S Y P H I L I S	Primary 1.4 per 1,000 admissions	11 per 1,000 admissions
	Genital lesions only	Mostly genital lesions
	Secondary 0.9 per 1,000 admissions	269 per 1,000 admissions
	Genital with or without extra-genital lesions	Extragenital, mostly with genital lesions
	Combined primary and secondary	39 per 1,000 admissions
	Lymphogranuloma 5.2 per 1,000 admissions	34.4 per 1,000 admissions
	Granuloma inguinale 0.4 per 1,000 admissions	6.9 per 1,000 admissions
	Chancroid 0.8 per 1,000 admissions	9.1 per 1,000 admissions
	Condylomata acuminata 2.0 per 1,000 admissions	
	Bartholin abscess 30.6 per 1,000 admissions	

On the dermatologic service at Bellevue Hospital, the incidence of syphilis in female patients is 48 per cent. Primary syphilitic vulvar lesions were encountered in 11 per 1,000 female admissions and secondary manifestations in 269 per 1,000. The largest number of these patients had both generalized and genital evidences of the disease. Lymphogranuloma occurred in 34.4 per 1,000, granuloma inguinale in 6.9 per 1,000, and chancroid in 9.1 per 1,000, one-half of these latter cases presenting only a Ducrey infected inguinal bubo.

TABLE II. REPORTED CASES OF VENEREAL DISEASES, HEALTH DEPARTMENT

Females, all ages; New York City, 1940

	TOTAL REPORTED CASES	PRIMARY LESIONS	SECONDARY LESIONS
Syphilis	13,780	264	777
Lymphogranuloma	75		
Granuloma inguinale	15		
Ducrey infection	8		
Gonorrhea	3,888		

An impression of the prevalence of these diseases in New York City may be obtained from a survey by the Department of Health² (Table II). During 1940 there were 13,780 reported cases of syphilis occurring in females of all ages. There were 264 primary lesions, most of which

were on the genitals, and 777 secondary lesions, many with genital manifestations. During the same period there were 75 cases of lymphogranuloma reported, 15 of granuloma inguinale, 8 of Ducrey infection, and 3,888 of gonorrhea.

GONORRHEA

The characteristic picture of acute or chronic vulvovaginitis of childhood is too well known to necessitate its further description. In the adult, however, skin manifestations about the genitals are not the rule and secondary involvement, notably a dermatitis, is the result of irritating discharges and lack of cleanliness. These skin findings when present either in the child or adult offer no pathognomonic criteria for diagnosis, since nonspecific infections may cause a similar clinical picture. Thus the presence of a foreign body in the vagina, irritating urine, lack of cleanliness, and intestinal parasites, as well as the vulvitis arising with acute exanthemas, require differentiation in the child; while monilia and trichomonad infections, as well as other instances of simple vulvitis, must be considered in the adult. An infrequently encountered inguinal bubo due to the gonococcus has been described by Greenblatt and associate.³ Usually unilateral this bubo resembles the chancroidal infection. It goes on to suppuration and the aspirated pus reveals occasional gram-negative intracellular diplococci. The presence of the gonococcus was further confirmed by culture and biochemical tests.

SYPHILIS

The incubation period may vary from three to four weeks frequently but by no means is it always followed by an observed primary lesion. This disease with its protean manifestations may produce a genital primary lesion which abides by no rule, varying from a simple small erosion to the characteristic hard chancre. The chancre while usually single may occasionally be multiple. As observed in this study, the following sites are given in their decreasing order of frequency: fourchette, labia majora, labia minora, urethra, perineum, vagina, thigh, and mons veneris.

Chancres of the fourchette are usually single and diamond or irregular in shape. They are most often of the erosive type, being rather superficial with a yellowish or grayish red surface. Induration of the base is most often lacking. The borders while being sharply demarcated, are not undermined, being on a level with the surrounding skin. The patient will often ascribe this lesion to traumatism resulting from forcible coitus. The typical hard indurated chancre is less frequently found here.

On the labia majora, the erosive type of chancre is the most common. It is usually round or oval, generally single, but may be multiple with a finely demarcated border which is not raised and the base is most frequently not indurated. Its surface is reddish like raw meat, reddish brown, or less often grayish. Chancres are usually painless. The ulcerative chancre of the labia majora is the typical hard chancre with its round or oval ulceration, well-defined border which may be raised and an excavated indurated base which may be covered with a grayish membrane or tenacious wash leather slough. At other times the base is raw ham colored. The least common variety is the papular chancre. It is a red, raised, flat plateau-like papule which differs from the secondary manifestations, in that the papular chancre is usually singular

and has an indurated base. Edematous induration in adjacent tissue may be observed with either type of chancre more frequently, however, with the ulcerative type. Inguinal adenopathy, the "satellite bubo," is very often but not universally found with primary syphilitic lesions about the external genitals, but when it does occur it is characteristic, in that it is painless, bilateral with discrete nodes, rubbery in consistency, and devoid of any acute inflammatory reaction unless there is an associated mixed infection.

Labia minora chancres are most frequently characterized by an indurated base with edematous induration of the loose connective tissues of the labia adjacent to the chancre.

Chancres of the urethra and clitoris are most often of the ulcerative type with the distinct hard chancre characteristics. Intraurethral chancres may produce a serous or blood-stained discharge, thereby differing from the discharge produced by a gonorrheal urethritis which is purulent.

One must ever be mindful of the possibility of a syphilitic infection when lesions appear upon the female external genitals, since there is such a variation in the appearance of the primary lesion. Therefore dark-field studies should be made on all genital lesions. The *Spirochaeta pallida*, with its spirals of marked brilliancy and regularity as well as its characteristic slow motion always maintaining its tight twist, differentiate it from the *Spirochaeta refringens* and the *Treponema genitalis*. The former is less rigid and less brilliant, the latter smaller, less brilliant, more irregular and more translucent than the *Spirochaeta pallida*. This dark-field procedure has its greatest diagnostic value during the first few weeks of the chancre when serologic tests are still negative. Subsequently the reverse is true.

The secondary manifestations of syphilis fortunately offer less difficulty in diagnosis. The condylomata lata or flat warts are raised plateau-like papules with a moist surface always swarming with spirochetes. They are multiple and variable in size, being usually discrete but sometimes confluent. The surface instead of being flat may be dimpled and its grayish color is due to surface dead epithelium. As this is rubbed off the color becomes more pinkish to coppery red. After a short time particularly in the absence of compression, these plateau-like surfaces may become rounded and nodular. One should look for associated generalized adenopathy as well as other secondary skin and mucous membrane manifestations. The results of serologic tests are now consistently strongly positive.

Tertiary gummatous lesions about the genitals are infrequently found and may be mistaken for carcinoma.

CONDYLOMATA ACUMINATA

Common usage of the term condylomas for both the flat and pointed varieties may cause some confusion. Condylomata acuminata should ordinarily offer no difficulty in diagnosis. These discrete papillomatous growths occur about the genitals, probably due to a virus infection associated with discharge and moisture. When small or moderate in size they appear as pedunculated fir tree-like projections. They sometimes grow into larger papillomatous masses the size of a clenched fist or a fetal head. The pedicle persists but grows much wider, and the surface may lose its thorny character, becoming more cauliflower-like in appearance. The occasional difficulty in diagnosis may be encountered

where both types of condylomata exist, the initial lesion being the lata with a superimposed acuminata. Where the mixed type is present, dark-field examinations, even though repeated, may not always yield the *Spirochaeta pallida*. However, at this time results of serologic tests are strongly positive. Last, the larger condylomata acuminata must be differentiated from an evverting carcinoma. In the latter instance, ulceration, friability, and necrosis of tissue with bleeding are extremely suggestive and biopsy yields a distinct picture of malignancy.

CHANCROID (SOFT CHANCRE, ULCUS MOLLE)

After a three- to eight-day incubation period, infection with the Ducrey bacillus causes either a single or more frequently multiple ulcerations, the borders of which are irregular but sharply circumscribed and undermined. The base is dirty grayish or yellowish in color and covered with a granular uneven surface. The ulcer bleeds readily and has a profuse purulent discharge capable of producing an associated vulvitis. There is usually no induration and the lesion is frequently painful. A red areola surrounds the ulcer. Since the lesions are auto-inoculable they are more likely to be multiple. When secondarily infected, phagedenic characteristics will ensue. As the result of inguinal lymph node involvement which takes place in one-third of the cases of Ducrey infection, the glands become acutely inflamed, frequently going on to suppuration. The bubo is usually unilateral and unilocular, tender and painful with surrounding erythema.

A diagnosis of chancreoid should never be made without excluding syphilis not only because the lesion cannot be differentiated clinically but because a combined infection may be present. The original soft chancre precedes the hard syphilitic one, since the incubation period of the former is so much shorter. Suggestive characteristics of the superimposed hard chancre make themselves manifest only after the first few weeks of the chancreoid.

The diagnosis of chancreoid may be suspected in the presence of reasonably characteristic lesions, being confirmed by one of the following procedures. A positive smear of Ducrey bacilli may be obtained from material taken with a loop under the edge of the ulceration and stained preferably with the Unna-Pappenheim stain. The characteristic streptobacilli are not always readily demonstrable; however, up until recently the autoinoculability of this lesion served as a diagnostic aid. Now a saline suspension of inactivated Ducrey bacilli has been employed as an intradermal test.⁴ One-tenth cubic centimeter of this bacillary antigen is injected intradermally, and within forty-eight to seventy-two hours a papule, pustule, or an indurated area of at least 7 mm. with an associated erythematous zone of at least 14 mm. will develop. This diagnostic procedure will become positive eight to fifteen days following the development of the ulcer and may remain positive for life. Therefore, a positive Ducrey skin test will not of necessity indicate the causative factor of the present existing lesion.

Syphilis when combined is diagnosed by repeated dark-field examinations and serologic tests. Even though spirochetes are not obtained after several attempts, serologic tests must be repeated for several months. These procedures should be done on all cases of known Ducrey infections.

The use of sulfanilamide in the treatment of chancreoid has now been definitely established.⁵ Not only is it of value for the original ulcerations but for the associated bubo as well.

GRANULOMA INGUINALE (GRANULOMA VENEREUM, GRANULOMA PUDENDI,
GRANULOMA INGUINALE TROPICUM)

Greenblatt and associates⁶ have successfully inoculated Donovan bodies producing granuloma inguinale in 4 cases. Such experimental work has helped to establish this protozoan as the causative factor for this disease, even though culture of the Donovan body cannot be accomplished as yet. After an incubation period of three to six weeks, the process starts as a small papule with superficial ulceration spreading peripherally in an irregular budding fungating fashion. Thus, from the external genitals the ulceration may extend onto the thighs, perineum and perianal regions. There is little or no tendency to heal as peripheral advancement takes place. The borders are rolled and the ulcerated surface itself presents a red granulating appearance. This condition is essentially a skin disease without lymphatic involvement. Therefore a true inguinal bubo is not encountered as long as a pyogenic infection is not superimposed. Pseudobubo, though infrequent, may be observed. These are simply subcutaneous granulomas which are nonsuppurative and appear as swollen nodules, ulcerating subsequently through the overlying skin, thereby causing the characteristic pinkish or reddish granulating ulceration.

The cervix is not infrequently the seat of this characteristic ulceration. Clinically it may be readily mistaken for an early carcinoma.

Where, in addition to the granulating ulceration on the external genitalia, enlargement of the parts and fistulas occur, granuloma inguinale may closely simulate lymphogranuloma. The two may also be combined.

The diagnosis is established by finding the Donovan bodies and the pathognomonic cells. Material is obtained by scraping the edge of the lesion. This is stained with the Wright or Giemsa stain. Tissue obtained for biopsy may be thinly rubbed on a slide which can be stained similarly. The biopsy itself may be employed. These preparations when positive yield the pathognomonic cells with foamy cytoplasm, causing intracytoplasmic cysts around which are found the deeply staining Donovan bodies.

Fuadin or Tartar emetic has been used with fairly good results in the treatment of granuloma inguinale. Surgical excision of the entire area or solid carbon dioxide pencil applications are therefore not resorted to very often.

LYMPHOGRANULOMA VENEREUM (CLIMATIC BUBO, TROPICAL BUBO, NICOLAS-FAVRE SYNDROME, LYMPHOGRANULOMA INGUINALE, LYMPHOPATHIA VENEREUM, ESTHIOMENE)

Much confusion has arisen not only because of some clinical similarity of this disease process and granuloma inguinale but because of the similarity in the nomenclature. The numerous synonyms for these diseases have not helped this confusion. The two diseases have an entirely different pathologic basis. Granuloma inguinale is simply a localized skin affection while lymphogranuloma venereum is essentially a disease involving lymphatic structures. Both are most often of venereal origin. The infectious agent, a filtrable virus, gains access through the skin of the genitals, producing an evanescent, apparently innocuous papule or vesicle comparable to a flea bite. This primary lesion does not always occur and when it does it may go unobserved.

The incubation period is about two or three weeks. Several weeks later, manifestations of the inguinal, genital, anorectal, or combined types are observed. Asymptomatic types are encountered.

The inguinal variety is most frequently found in men, since the inguinal and femoral nodes drain the site of the original inoculation on the penis. This lymphatic involvement is usually unilateral, sometimes bilateral. The glands are enlarged and painful, remaining characteristically discrete and multinodular. The overlying skin becomes adherent taking on a bluish or purplish red discoloration. Subsequently some of the nodules go on to suppuration, drainage occurring from numerous fistulous tracts. Aspirated material from this suppurating bubo is sterile for bacteria unless a mixed infection is present. All of the involved nodes do not necessarily go on to suppuration, however. The genital syndrome is found with greater frequency in the female either existing alone or combined with anorectal involvement. The initial lesion if noted may have occurred on the posterior vaginal wall or perineum and after a variable period of time, due to the lymphatic involvement, elephantiasis or enlargement of the external genitals takes place with or without ulceration. The elephantiasis is the result of inflammation and obstruction of lymphatic channels which is followed by hypertrophy and hyperplasia of the fibrous connective tissue. The resulting enlargement of the parts may be more or less symmetrical or there may arise pedunculated fibromatous nodules sometimes so large as to hang down between the thighs. When ulceration, though infrequent, is present with enlargement, the condition is known as esthiomene.

The anorectal syndrome may occur either alone or combined with the preceding type. This combination has been frequently noted in the cases studied. When the anorectal involvement occurs in the male, it is most often the result of direct implantation of the virus resulting from sodomy. In the female, the method by which these tissues become involved has been open to some dispute. Perhaps several routes are possible. Direct implantation may result from the infected vaginal discharge draining posteriorly over the perineum thereby reaching anal mucosa. Sodomy is another method. If, however, the primary lesion occurred near the fourchette or on the posterior vaginal wall, direct extension via lymphatics could involve the rectal wall which lies in fairly close proximity to the initially involved tissues. As the result of this extension, proctitis with subsequent stricture formation will develop. Lymphogranuloma venereum is accredited with being the most common cause of rectal stricture in the female. Fistulous tracts may also be found involving the rectum, vagina, and perineum.

A urethral syndrome has been described by Torpin and associates.⁷ In this present study, involvement about the urethral meatus was encountered in a few of the genital types. An elevation of the mucosa forming a plaque with or without ulceration may be found about the urethral orifice extending upward toward the clitoris. Pain and dysuria are the associated symptoms. In one of the cases of the present group, an associated carcinoma of the clitoris was considered because of the intolerable nocturnal pain. Urethral strictures do not occur.

The systemic manifestations of the disease are of variable frequency, being found more often with the inguinal variety, where at the onset fever, chills, and joint pains may be present. The genital and rectal varieties are more often encountered without these associated symptoms. Hyperglobulinemia is frequently observed.

While a tentative diagnosis of lymphogranuloma venereum may be made from the clinical characteristics, the Frei test, an intradermal skin test, must be employed to substantiate this diagnosis. The Frei antigen employed is the suspension of the virus-infected mouse brain which has been inactivated.⁸ Another antigen known as lygranum⁹ is obtained by inactivating the infected yolk sac of the chick embryo. Injecting $\frac{1}{10}$ of 1 c.c. of either of these antigens intradermally will produce a papule, vesicle, or pustule of at least 6 or 7 mm. in diameter in an infected individual. The associated erythema is of no significance and a control corresponding to the antigen employed must be injected so as to exclude protein sensitivity. The yolk sac control is less likely to produce a reaction than the mouse brain control. Positive skin tests will develop in ten to twenty-one days following the initial lesion and may remain positive for life. While Stein¹⁰ has produced reversal of the Frei test by treating patients with sulfanilamide, this has not been corroborated by others as yet.¹¹ Rake and his colleagues¹² have recently employed lygranum as the antigen in a complement fixation test. While adequate sensitivity may be present, the specificity of this test requires further study.

A pre-existing asymptomatic lymphogranuloma venereum with a positive Frei test may be present in a patient with a vulvar lesion of another origin or perhaps several etiologic factors may be combined. Therefore as a routine one must employ dark-field examinations, serologic tests for syphilis, smears for Donovan bodies, Ducrey bacilli and fusospirochetes. In addition to the intradermal Frei test, a similar test employing the bacillary Ducrey antigen must be done. A biopsy should be studied for evidences of Donovan bodies, tubercles, and tubercle bacilli as well as malignancy. This latter condition may co-exist with lymphogranuloma but is not as likely to be associated with granuloma.¹³ The biopsy may also be of value from the standpoint of a histologic differentiation of granuloma inguinale, lymphogranuloma venereum, and chaneroid.¹⁴

As the result of this routine the earliest lesion of lymphogranuloma venereum when observed can be differentiated from chancre and chaneroid; the later inguinal bubo of lymphogranuloma can be differentiated from syphilis and Ducrey infection; the genital syndrome can be differentiated from syphilis, chaneroid, granuloma inguinale, tuberculosis, and epithelioma; last, the anorectal syndrome can be differentiated from carcinoma and postoperative strictures.

Until recently, since no specific therapy exists, the treatment of lymphogranuloma venereum has been unsatisfactory. The use of the sulfonamide drugs (1 + 8) brought about marked improvement, particularly in the earlier more acute inflammatory phases of the disease. Frei antigen intravenously has been employed with fairly satisfactory results. However, the later elephantiasis and strictures have been much more resistant to therapy. The enlargement of the external genitals with or without pedunculated masses can only be relieved by surgery. For the proctitis, the sulfonamides, notably sulfaguanidine,¹⁵ have been of value. For the later stricture formation, Frei antigen intravenously and the sulfonamides and diathermy, either singly or in combination, are employed to soften and relax the stricture. In addition mechanical dilatation may be resorted to. Therefore colostomy is employed only when occlusion is progressive and obstructive manifestations ensue.

TUBERCULOSIS

Tuberculous lesions about the external genitals are very infrequently observed. Three types of lesions have been described.¹⁶ The first is the most typical, starting as a nodule and subsequently going on to ulceration. The margins are undermined and the granular base is covered with a dirty yellowish exudate in which at times grayish white miliary tubercles may be recognized. The lupus-like ulceration, when this type occurs, is recognized by the characteristic apple jelly nodules. Scrofulodermal ulcerations with indurated margins are to be found around tuberculous fistulous openings.

The diagnosis of a tuberculous ulceration can be made by the characteristic histologic picture. Tubercle bacilli may also be found in these tissues as well, but where the etiologic agent is in doubt, guinea pig inoculations must be resorted to.

CONCLUSIONS

A positive diagnosis should never be made solely on the appearance of infected lesions about the external genitals. Grossly similar lesions may result from different etiologic factors. A single agent may be capable of producing variable lesions. Combined infections may be present. Therefore, pathognomonic characteristics are lacking so that an unequivocal diagnosis can be established only by the employment of certain routine procedures. These must include dark-field examinations and serologic tests, smears for Donovan bodies, Duerey bacilli and fusospirochetes, intradermal tests with the Duerey bacillary antigen and the Frei antigen, and last microscopic examination of tissue obtained for biopsy.

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THE END RESULTS OF THE SIMPSON OPERATION IN SIXTY-ONE PATIENTS DELIVERED AT TERM

WITH REMARKS ON THE TREATMENT OF RETROFLEXIOVERSION IN THE CHILDBEARING WOMAN

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SIGNIFICANCE OF RETROFLEXIOVERSION

IN THE past many suspension operations have been performed for the relief of symptoms in patients having simple retroflexioversion of the uterus. As the evidence of failures accumulated, gynecologists began to appreciate the influence of constitutional types, and critical analysis of the asthenic woman led to a far better interpretation of her complaints.

The idea that a retroflexioversion of the uterus necessarily produces symptoms and requires treatment is no longer entertained. Such symptoms as lower abdominal pain, backache, dysmenorrhea, and uterine bleeding originate so often in functional or extragenital disorders, that only the unwary will now ascribe them to retroflexioversion until all other possibilities of origin have been explored.

INDICATIONS FOR TREATMENT IN THE CHILDBEARING WOMAN

Retroflexioversion acquires a new significance, however, in the child-bearing woman, and in the majority of them, at some time requires attention. It may interfere with conception; it is one of the most frequent causes of abortion in the early months of pregnancy; it may be responsible for backache, lower abdominal pain, and almost any pelvic symptom in the woman who has gone through pregnancy and labor.

THE CHOICE BETWEEN POSTURAL, PESSARY, AND OPERATIVE TREATMENT

Postural treatment with the knee-chest and the Sims' positions alone or combined with the support of the uterus by a Smith pessary are completely satisfactory in a large proportion of patients; conception is promoted, abortion is prevented, backache and lower abdominal pain are relieved.

There are several advantages in postural and pessary treatment:

1. It saves the hospitalization and the risk of morbidity and mortality attending an abdominal section.

2. The young mother is not taken away from her children and the home duties that loom so important.

3. It settles definitely the role of the pelvic lesion in the symptomatology.

4. It may be curative when a Smith pessary (Findley model) is placed in situ within two weeks of delivery and the round ligaments shorten enough during involution to maintain the uterus.

Operative treatment may be elected when:

1. The promptness of an operative cure has much appeal and is greatly to be desired.

2. There is need also of appendicectomy, myomectomy, salpingectomy, or oophorectomy.

3. The patient is opposed to postural treatment, fretting at the care which she must exercise herself and the occasional medical attention.

4. Adhesions prevent replacement of the uterus or extreme relaxation of the pelvic floor makes a comfortable fitting with the pessary impossible.

5. The patient has her complement of children and intends to adopt contraceptive measures, the troublesome symptoms continuing when the uterus is unsupported.

THE REQUISITES OF SUSPENSION OPERATIONS AND THEIR INFLUENCE ON TECHNIQUE

Suspension operations during reproductive years must entail no disadvantage during a subsequent pregnancy and labor, and the uterus must remain in good position. Complete accord has not been reached as to the preferable form of operation, there being many old and one or two new ones.

While the type of operation should depend finally upon the conditions at hand, there are certain fundamental principles to be observed whenever possible. They concern particularly the decision as to which part of the round ligament is to be selected as the medium of suspension.

In explanation of the fact that the inner part arising directly from the fundus of the uterus is preferable, attention may be directed to its muscular structure, resembling the uterine wall, in contrast to the outer part which becomes less muscular as it approaches the inguinal canal and there quite fibrous.

The round ligaments hypertrophy early in pregnancy, later elongate as the wall of the uterus thins out to accommodate the growing products of conception (uterine wall 8 mm. at start, 25 mm. by fourth month, 4 to 7 mm. at term, DeLee), and shorten after labor in concurrence with the involution of the uterus. The inner parts of the ligaments participate more actively in these changes than the outer parts since they contain more muscular and less fibrous tissue.

Operations that use the inner part of the round ligaments as the suspensory medium have been described by Olshausen, Gilliam, Simp-

son, Montgomery, Bissell, and many others. The ligament is not sewn to the uterus; in a subsequent pregnancy there is no interference with the normal enlargement of the uterus, and after labor the ligament along with the uterus returns by involution to its former dimensions.

When the outer part of the round ligament becomes the suspensory medium as in the Webster-Baldy,^{3, 11} Coffey,⁴ and other operations, the reduplicated inner part of the ligament having been sewn to the uterine surface, there is interference sometimes with the increase in the size of the uterus during early pregnancy. Although the more fibrous part of the ligament elongates as the uterus rises out of the pelvis, it participates less actively in the early muscular hypertrophy and the late muscular involution, and therefore does not so uniformly return to its pregestational state.

THE SIMPSON OPERATION

There are certain advantages of the Simpson technique over the earlier operations of Olshausen and Gilliam. Simpson, in 1903, was the first to propose that the shortening of the round ligaments should be retroperitoneal; Montgomery described his plan which was quite similar in 1905.

1. The ligament is carried extraperitoneally to the fascia of the abdominal wall and does not directly traverse the peritoneal cavity or create three passageways, one central and one on each side in which intestinal coils may become incarcerated.

2. The uterus itself is not attacked, and there are no raw or sutured surfaces left upon it to invite adhesions.

3. The fastening of the ligament to the bared fascia of the abdominal wall with linen sutures is conducive to a durable attachment.

In Simpson's original paper he called attention to another factor in the end results of his operation and others of its kind; the support is more directly upward and forward. In the Coffey and the Webster operations, it is partly lateral. The straight line of support is stronger than the curved one.

In our own practice we have facilitated the performance of the Simpson operation and avoided the traumatism of various forms of forceps by the use of a special round ligament carrier (Fig. 4), and promoted security in the fixation of the ligament by using three interrupted sutures of fine linen instead of one figure-of-eight suture (Figs. 1 to 3). A full description of the technique of the operation will be found elsewhere.² Figs. 1, 2, and 3 may be sufficiently descriptive.

Operations on the cervix and perineum are often needed in combination with suspension operations, and the same is true of uterosacral shortening when there is definite descent of the cervix.

Many papers have been written concerning the late results of various forms of suspension operations so far as the relief of symptoms and the maintenance of normal position are concerned, but very few deal at any

length with the influence of the operation upon a subsequent pregnancy or with the position of the uterus after labor. In the childbearing period these are the important questions, for if an operation of a certain technique were to interfere quite commonly with the course of a subsequent pregnancy and labor, or if the uterus was likely to become displaced again after the stress of these two processes, then it would fail in its requisites.

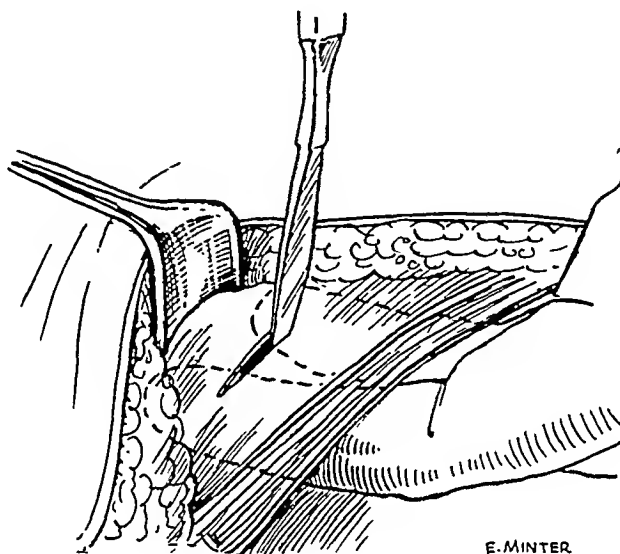


Fig. 1.

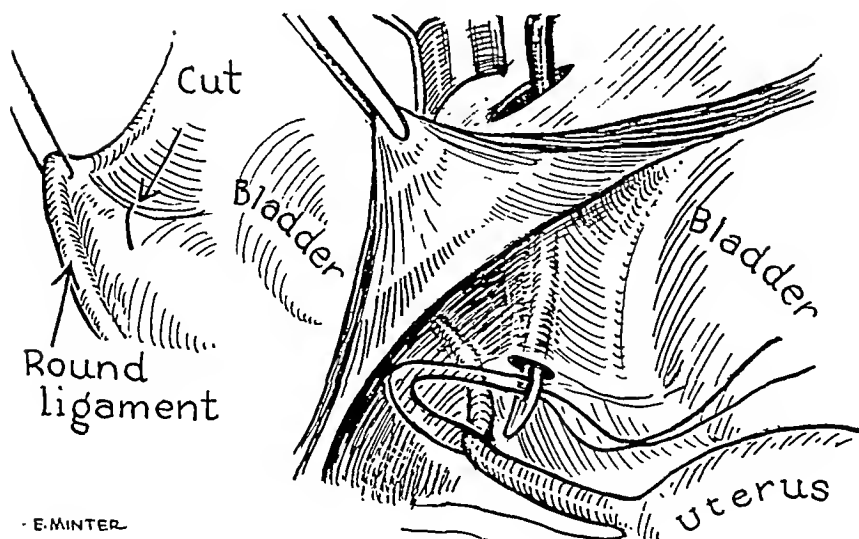


Fig. 2.

RESULTS OF SIMPSON SUSPENSION AFTER SUBSEQUENT PREGNANCY AND LABOR

To provide information of this sort in respect to the Simpson technique, we have reviewed our ward and private patients at the Jefferson

and the Bryn Mawr Hospitals and included those of Drs. Lewis C. Scheffey, James L. Richards, Charles Lintgen, and Thomas Costello.

Altogether there were 500 patients covering a period of twenty years. There were 4 operative deaths (Table I). During the performance of the operations on two occasions, the veins of the broad ligament were injured. In one patient, salpingo-oophorectomy was required; in the other, nothing more than simple ligation of one of the veins was necessary.

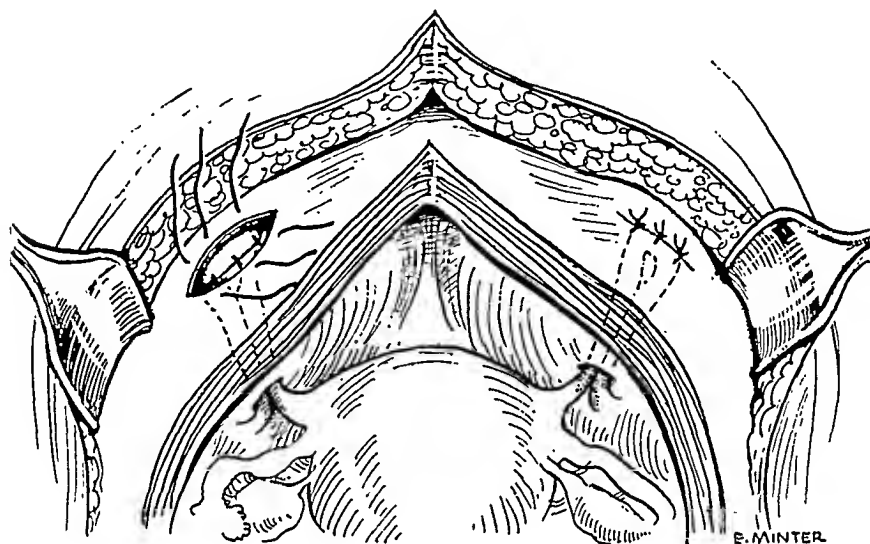


Fig. 3.

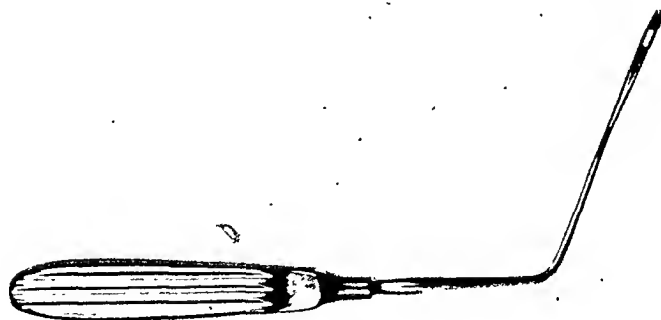


Fig. 4.

The number of patients in whom pregnancy followed the operation was 76 (Table II). There are certain facts which are explanatory of this comparatively small number.

In a group of 50 patients the indications for operation were not concerned with the promotion of childbearing nor were the symptoms the result of pregnancy or childbirth. The operations in this group of patients were performed with the desire of relieving troublesome symptoms; in some with well-marked organic lesions in association with the retroflexioversion, and in others after careful study and the conclusion that the uterus must be put into normal position.

TABLE I. TOTAL NUMBER OF SIMPSON OPERATIONS 1921-1941 (500)

Operative deaths	4	
Heat stroke		1
Cerebral hemorrhage		1
Pulmonary embolus		1
Peritonitis		1
Mortality 0.8 of 1 per cent		

TABLE II. PATIENTS PREGNANT AFTER SIMPSON OPERATION (76)

Delivery at term natural passages	56
Cesarean section at term	5
Patients aborting (2 by induction) and not delivering at term	11
Patients pregnant Jan., 1941, no information since	3
Patient pregnant in 1936, no information	1

TABLE III. POSITION OF UTERUS AFTER DELIVERY AT TERM

Uterus in normal position after delivery at term	58
Uterus in retroversion and descensus of first degree	3
Patients examined personally	43
Reported by obstetrician	15
Reported by family doctor	3

Fifty-eight patients were sterilized by ligation or excision of the tubes; of the remainder, many of the women used contraceptive measures and many were nearing the menopause.

Abortion occurred in 11 patients; not one in this group ever went to term; in 2 the abortion was induced, in one as a therapeutic measure for psychosis; in the other on account of serious domestic troubles ending in divorce. There was a total of 12 abortions in 10 patients; the eleventh patient had had 6 abortions, but there were no deliveries at term before the operation; after the operation she had six more abortions but one successful delivery at term.

Bearing in mind the statement of Litzenberg, who reviewed the literature, that "the proportion of one abortion to five viable births is supported by authorities from many countries," we may conclude that the altered anatomic relations brought about by the operation did not predispose to abortion. On the contrary we have a definite number of patients in whom the performance of the Simpson operation after failure of postural and pessary treatment put an end to a repetition of abortion in early pregnancy.

Among the 61 patients who were delivered at term, 5 cesarean sections were performed. We must regard this as a high proportion, but an analysis of the conditions that obtained in each patient seems to show that the indications for the cesarean section were not the result of the previous operation.

CASE REPORTS OF CESAREAN SECTIONS

CASE 1.—Miss A. D., aged 15 years, of the asthenic type, complained of leucorrhea, backache, and pain in right lower abdomen. Subjected to operation only after every other effort to relieve pain had failed. Dis-

charging Skene's tubules; endocervicitis; Neisserian infection suspected but not proved. Exeision of Skene's tubules; Pozzi's operation for drainage; Simpson's operation and appendicectomy in 1923. She was married eleven years later; uterus in normal position. At term 1934; there was disproportion due to small pelvic diameters. Cesarean section was selected as the procedure of choice. Examination in 1935, uterus in normal position.

CASE 2.—Mrs. V. G., aged 22 years, married for two years, one six weeks' miscarriage five months after marriage; desired children. Had backache. Objected to pessary. Had a slightly enlarged and prolapsed right ovary. Simpson operation in 1938. At term in 1940; large baby occiput posterior; patient had grown stout; was thick set; bore pain badly; an unfavorable obstetric subject for delivery through the natural passages.

CASE 3.—Mrs. M. H., aged 30 years; 3 induced miscarriages previously, curettage after each one; the last in 1929. Simpson operation for retroflexioversion and adhesions in 1932. Pregnancy and subsequent easy delivery with forceps at the outlet in 1931, but the child died on the eighth day from atelectasis and pneumonia. Second pregnancy in 1937. At term had bleeding; diagnosis of premature partial detachment of placenta or marginal placenta previa. Continuous and increasing loss of blood; rise in fetal and maternal heartbeat.

CASE 4.—Mrs. H. R., aged 26 years; one child; backache and pain right lower abdomen; Simpson operation in 1932; cesarean section in 1933, after twenty-four hours of labor at term, no engagement and evident disproportion.

CASE 5.—Mrs. F. B., aged 25 years; 3 children. Bearing down pain; Simpson operation in 1927; one full-term normal labor in 1929; cesarean section in 1933; four living children already and desired to be sterilized.

Aside from the cesarean sections, there was nothing unusual in the delivery of the other patients. They were either spontaneous or forceps deliveries with a fetal mortality of two (Mrs. H. M., and Mrs. M. D.).

The uterus remained in normal position in 58 out of 61 patients (95 per cent cures, 5 per cent recurrencees) examined after a subsequent labor (Table III). In the patients classed as failures (3), the retroversion and descent was little if any more than the first degree. The fundus of the uterus was definitely held up. In each one there had been much damage to the pelvic floor.

For two of the patients classed as recurrencees, a plastic operation was performed and the round ligament shortening was repeated; the third patient has had no symptoms.

CASE REPORTS OF REPEATED SUSPENSION OPERATIONS

CASE 6.—Mrs. B. D., aged 35 years; miscarriage of six months' twins a year after marriage. One healthy child at term two years later. Desired another conception. Had pain in the right lower abdomen; pessary for awhile; Simpson operation in 1923. Spontaneous delivery in 1925. Complained of many symptoms; psychoneurotic; general health subject of much concern; cystocele, rectocele, relaxed pelvic floor, the uterus

tending slightly to retrovert and sag, not retroflexed, still supported to considerable extent by attached round ligaments. Second operation in 1926, plastic and repetition of round ligament shortening; one pregnancy since; miscarriage at three months in May, 1927; psychosis increased; the uterus in normal position, January, 1928.

CASE 7.—Mrs. M. D., aged 27 years; one child within two years of marriage; miscarriage in April, 1916. Complained of backache; trial with pessary unsuccessful; Simpson operation in 1916; spontaneous delivery of nine-pound child in 1918; another very difficult delivery in 1920; child said to weigh twelve pounds, born dead. Large cystocele and rectocele later with cervix within an inch of the vaginal introitus but the fundus well forward. Wore pessary from 1923 to 1927; continued to complain and wanted operative relief. Plastic and Simpson operation in 1927. Examination two months later, satisfactory result.

CONCLUSIONS

1. During the childbearing age, treatment of retroflexioversion of the uterus may be required: (a) to promote conception, (b) to favor the normal course of pregnancy, (c) to relieve various symptoms, the most frequent of which are low abdominal distress and backache, worse in the erect posture and upon exertion, better when lying down.

2. The procedure of choice is postural (knee-chest and Sims' positions) followed by manual replacement and the fitting of a Smith pessary. An exception should be made when the condition is discovered for the first time in early pregnancy. Nothing more than postural and very gentle efforts at bimanual replacement are needed in the great majority of cases. The manipulation incident to the formal fitting of a pessary during early pregnancy may provoke abortion.

3. The relief afforded by the pessary proves the role of the lesion in the production of symptoms.

4. When the uterus is in good position within two weeks of labor and the patient is fitted with Findley model pessary and wears it for three months, there is a small but definite chance of cure.

5. When the patient wishes prompt and permanent relief and when the pessary is uncomfortable or fails to hold the uterus, recourse may be had to operation.

6. The operation must be of such a type that there is no disadvantage to the patient during a subsequent pregnancy and labor, and the prospect of recurrence of the displacement after labor is very small.

7. The Simpson operation gives almost uniformly satisfactory results. Of 61 patients delivered at term, 58 were cured (Table III).

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STRICTURE-FORMING LESIONS OF THE FEMALE GENITALS AND RECTUM*

A YEAR'S STUDY OF CASES IN THE DISTRICT OF COLUMBIA

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THE purpose of this study is threefold: first, to discuss the development of facilities for a complete diagnostic investigation of hypertrophic-, ulcerative-, sinus-, bubo-, and stricture-forming lesions of the female genitals and rectum; second, the controlled use of accepted and newer forms of therapy, so that improved results might be obtained; third, the establishment of the relative incidence of lesions of this type in the District of Columbia.

A carefully detailed history was taken and a complete physical examination was performed in each case. All patients were subjected to serologic tests for syphilis, dark-field examinations, intradermal tests, biopsies, smears, fresh preparations, cultures, and hemograms. After the clinical diagnosis was established proper therapy was instituted. Every effort was made to keep each patient under close observation.

A series of 117 consecutive cases is presented in order of incidence. The various tests and procedures employed will be discussed only so far as proper interpretation for correct diagnosis is concerned.

In a high percentage of the patients examined associated and related diagnoses were made (Table I). Many of the patients were suffering from two or more venereal or related diseases. Discussion, however, will be limited to the primary diagnosis of the lesions.

LYMPHOPATHIA VENEREUM

Lymphopathia venereum was found in 34, or 29 per cent, of the patients. Of the commonly used terms to designate this disease, our personal preference is lymphopathia venereum.

*Presented at a meeting of the Washington Gynecological Society, January 24, 1941, Washington, D. C.

TABLE I. SHOWING VENEREAL LESIONS WITH ASSOCIATED DIAGNOSES

NUMBER OF PATIENTS	PRIMARY DIAGNOSIS OF LESION	ASSOCIATED DIAGNOSIS				
		SYPHILIS, GENERAL	POST- CHAN- CROIDAL STATE	PREG- NANCY	TRICHO- MONAS	GONOR- RHEA
34	Lymphopathia venereum	11	9	6	6	4
27	Genital syphilis					
	a. Primary	14		3	5	3
	b. Secondary	13				
18	Chancroidal infection	9		3	8	2
11	Granuloma inguinale	4	5	1	3	1
11	Condyloma acuminatum	4	1	5	7	1
6	Epidermoid carcinoma	3	1		1	
5	Nonspecific lesions	1			1	
3	<i>Trichomonas vaginalis</i> vaginitis			2	3	
1	Leucoplakia					
1	Tuberculosis					

The voluminous literature on lymphopathia venereum will only be reviewed to credit Hellerstrom and Wassen,¹ in 1930, with the identification of the etiologic agent and the introduction by Frei,² in 1925, of a specific skin test antigen.

When performing the skin test, we prefer the use of "bubo pus" and "mouse brain" antigens. In addition, we are testing the purified chick embryo propagated Frei antigens* together with chick tissue control.

Only patients without rectal strictures were retained in our series for treatment. Stricture cases were referred to general surgery.

Therapy in the retained group consisted of the sodium salt of sulfanilic acid orally,† and a 10 per cent solution intravenously as proposed by Hebb, Sullivan, and Felton.³ In cases under this treatment for four to six months, no decrease in vulval hypertrophy could be attributed to the use of sulfanilic acid. Vulvectomy was performed in seven cases. Operation was preceded by vulval hygiene. Repeated smears were made to determine the decrease in the bacterial flora and fusospirochetes. In the vulvectomy group, viewed at monthly intervals, areas of recurrence were noted in three patients. These areas resolved with further local hygiene and sulfanilic acid orally. The results obtained in this group were satisfactory.

The histopathology identified in six of the vulvectomy cases was characterized by an inflammatory reaction. There was a diffuse patchy lymphatic and plasma cell infiltration. The muscle fibers appeared split and pushed aside by the inflammatory change. There were perivascular collections of lymphocytes. Giant cells of the Langhan's type were found. Cytoplasmic inclusion bodies, noted by Gamma⁴ in 1923, were also seen in our tissue. The cellular infiltration was present in the seventh case, but there were no giant cells.

SYPHILIS

Syphilis of the female genitals was found in 27, or 23 per cent, of the patients. It should be noted that 50.4 per cent of all the patients studied had general syphilis, but only 23 per cent had genital syphilitic lesions.

*The purified chick embryo propagated Frei antigen together with chick tissue control was generously contributed by Dr. R. W. G. Wyckoff, Lederle Laboratories, Pearl River, N. Y.

†The sodium sulfanilate was prepared and contributed by Dr. L. D. Felton, Public Health Service, Washington, D. C.

Cases of this type were diagnosed only if the *Treponema pallidum* was demonstrated by dark-field examination, or if serologic tests were positive and all other etiologic agents were ruled out.

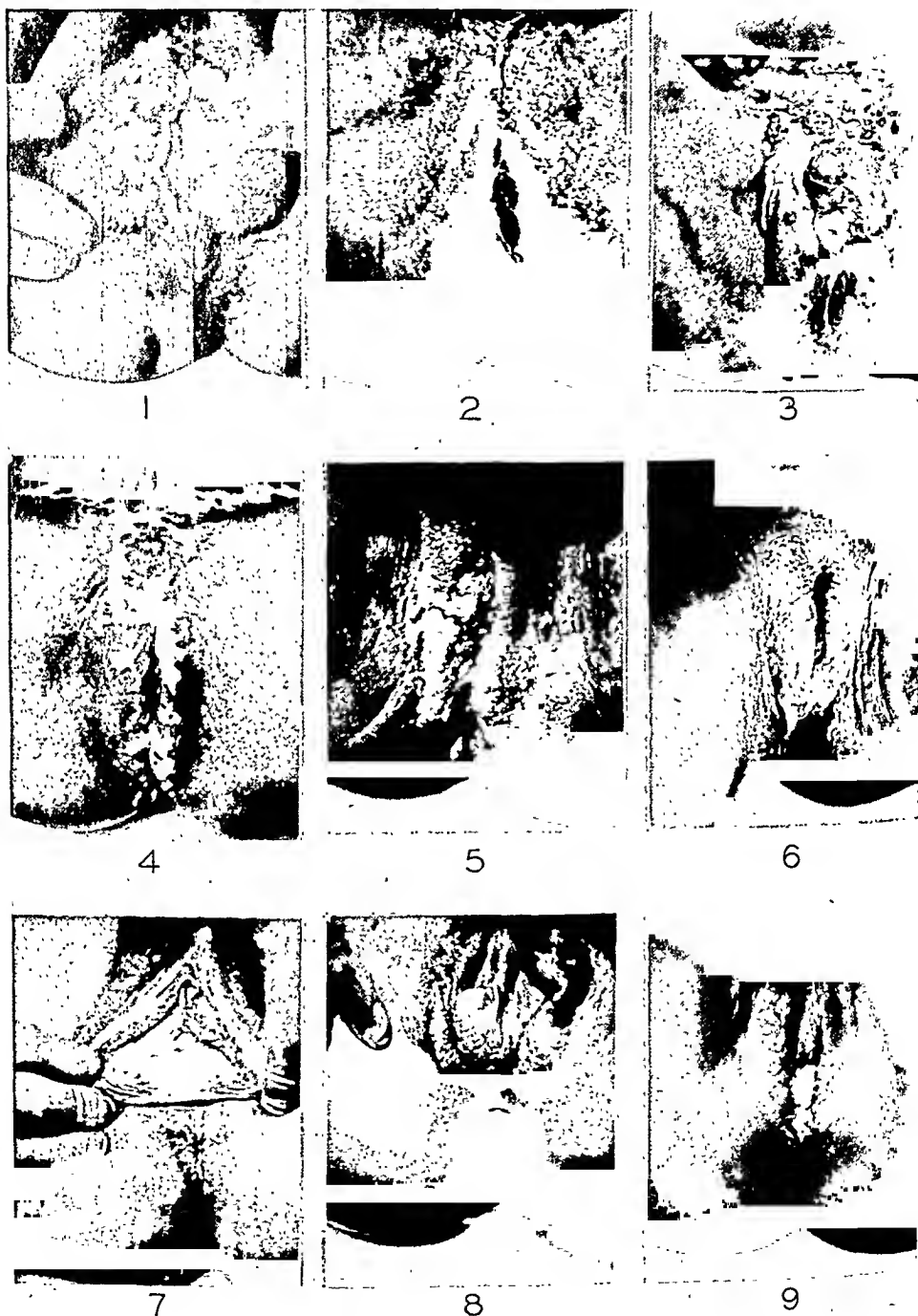
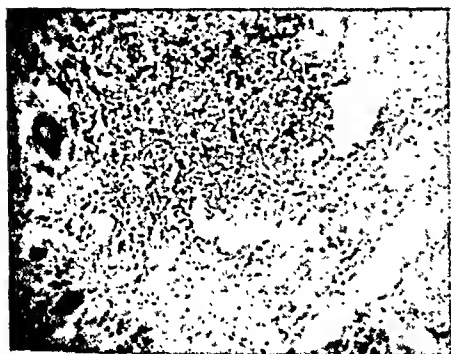


Fig. 1.—Lymphopathia venereum showing hypertrophy and ulceration of the vulva.
 Fig. 2.—Result following therapy and vulvectomy.
 Fig. 3.—Granuloma inguinale with hypertrophy of the vulva.
 Fig. 4.—Result following therapy and partial vulvectomy.
 Fig. 5.—Condylomata acuminata of the vulva.
 Fig. 6.—Result following therapy and fulguration.
 Fig. 7.—Chancroidal ulcer associated with pregnancy.
 Fig. 8.—Tuberculosis of the vulva.
 Fig. 9.—Result following vulvectomy.

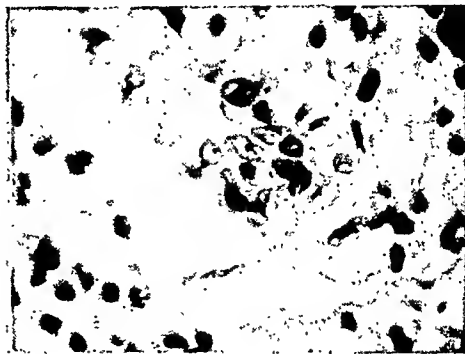
These patients were immediately hospitalized on the venereal ward for antisyphilitic therapy. The diagnosis was confirmed by the rapid regression of this type of lesion under specific therapy.

CHANCROIDAL INFECTIONS

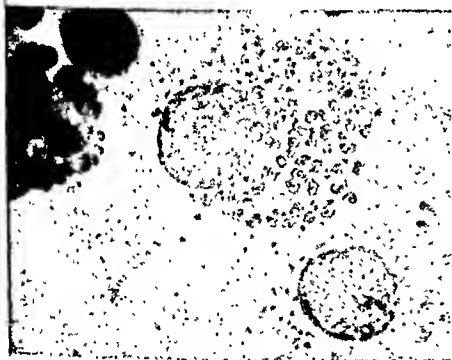
Chancroidal infection was encountered in 18, or 15.4 per cent, of the patients.



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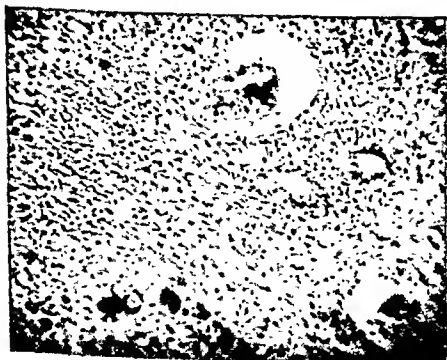
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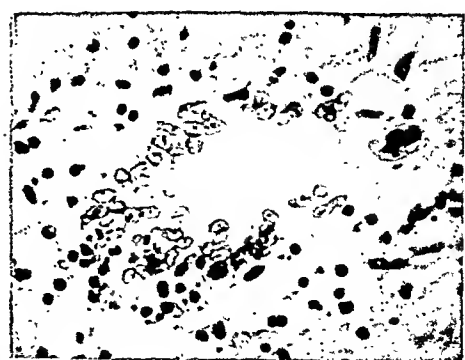
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Fig. 10.—Histopathology, Fig. 1, low power.

Fig. 11.—Histopathology, Fig. 1, high power.

Fig. 12.—Diagnostic cell with Donovan bodies (Fig. 3).

Fig. 13.—Re-epithelization following tartrate therapy (Fig. 3).

Fig. 14.—Histopathology, Fig. 8, low power.

Fig. 15.—Histopathology, Fig. 8, high power.

The diagnosis of chaneroidal infection was based on a positive intracutaneous test with Ducrey vaccine⁵ and exclusion of other causes. A noteworthy clinical point is that the discrete ulcer due to *H. ducreyi* is tender. This can be determined by pressure when slides are prepared with a sterile loop.

Although chaneroidal infection is self-limiting, sulfanilamide orally and locally hastens the healing process. A high incidence of *Trichomonas vaginalis*, associated with this lesion, was noted. Diagnosis of chaneroidal infection by smear has not been successful in our hands.

GRANULOMA INGUINALE

Granuloma inguinale occurred in 11, or 9.4 per cent, of the patients. The diagnosis of granuloma inguinale was based on the finding of Donovan bodies, response to therapy, and exclusion of other causes. In the search for Donovan bodies, smears were prepared from the biopsied tissue. The unfixed preparation was inverted into diluted Geimsa stain. Inversion resulted in decreased stain precipitation.

Biopsies prior to and during therapy revealed the histopathologic picture noted by Pund and Greenblatt.⁶

Under therapy, healing of extensive lesions resulted in partial pigmentation, a fact noted by Giglioli.⁷ Williamson⁸ stated that the scar always remains depigmented.

Following clinical healing, we recommend plastic surgery to correct vulval deformities. The identification of Donovan bodies in this excised re-epithelized tissue is viewed as a source of relapse. For this reason, patients should receive tartar emetic and fuadin for several months after clinical healing has occurred.

The importance of a complete diagnostic survey is again emphasized in this group. The finding of five patients who reacted to the bacillary antigen of Ducrey, yet on further examination, proved to have granuloma inguinale, proves the value of a complete study in each case. Initial medical treatment consists of tartar emetic intravenously and fuadin intramuscularly.

CONDYLOMA ACUMINATUM

Condyloma acuminatum appeared in 11, or 9.4 per cent, of the patients. Condyloma acuminatum was diagnosed from its clinical appearance, exclusion of other diseases, and by biopsy. Again a high incidence of *Trichomonas vaginalis*, 63.7 per cent, was associated with this type of lesion.

Treatment has consisted of vaginal and vulval hygiene until trichomonads, fusospirochetes, and other organisms were reduced to a minimum. When cleanliness of the lesion, as measured by smears and cultures, warranted, the condylomas were removed by fulguration.

EPIDERMOID CARCINOMA

Malignant disease of the vulva was found in 6, or 5.1 per cent, of the patients.

In two of these patients referred for study, the Frei reaction was regarded as positive by other observers. In our hands, the Frei tests were negative. Biopsy confirmed the paramount diagnosis. Hence, a positive Frei or Ducrey test does not preclude the presence of a malignant lesion. *We stress the importance of biopsy even though other tests may be regarded as positive.*

NONSPECIFIC LESIONS

Nonspecific lesions were encountered in 5, or 4.3 per cent, of the patients. They comprised chronic inflammatory tumors, inguinal adenitis, and one ulcer. Treatment based on the exclusion of all possible factors was symptomatic.

TRICHOMONAS VAGINALIS VAGINITIS

This single protozoan vaginal infestation, associated with multiple superficial ulcers of the vulva, was encountered in 3, or 2.6 per cent, of the patients. The relationship of the protozoan to the vulval ulceration may be regarded by some as controversial, but all other causes were excluded. Two cases occurred with pregnancy. The ulcers resolved under antiprotozoacidal therapy.

LEUCOPLAKIA OF THE VULVA

Leucoplakia was encountered in only one patient. Vulvectomy was resorted to as a therapeutic measure. The histopathologic picture is well established.

TUBERCULOSIS OF THE GENITALS

One case of hypertrophy and ulceration of the vulva is presented as tuberculosis of the genitals. The case, in every respect, qualified as lymphopathia venereum, but one acid-fast bacillus morphologically like *M. tuberculosis* in a giant cell was noted by a competent observer. No other focus was elicited. This is only suggestive evidence that the lesion was due primarily to *M. tuberculosis*. All lymphopathia tissue is now cultured for this organism. Vulvectomy produced a good result.

SUMMARY

1. Attempts have been made in the District of Columbia, at Gallinger Municipal Hospital, to develop facilities for the diagnosis and treatment of lesions of the female genitals.
2. The use of sodium salt of sulfanilic acid in the treatment of lymphopathia venereum has been discussed.
3. Corrective surgical procedures can be utilized in lymphopathia venereum of the vulva, the healing phase of granuloma inguinale and in the papillomatous growth of condyloma acuminatum.
4. We have not necessarily explored new fields but have applied established diagnostic procedures. Only in this way can a higher percentage of correct diagnoses be made and proper therapy instituted.

The authors wish to thank Dr. Bayard Carter and C. P. Jones of Duke University Hospital, Durham, North Carolina, for many personal communications, and great material aid during this study; Dr. H. H. Leffler, Gallinger Municipal Hospital for help in pathology; Dr. George G. DeBord, District of Columbia Health Department, for cultural procedures.

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A STUDY OF 569 CASES OF ENDOMETRIOSIS*

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WITHIN recent years the condition known as endometriosis has been the object of much discussion and extensive investigative work. As a result of this growing interest, we have made great strides toward the more intelligent diagnosis and treatment of the condition. There are, however, many problems still remaining which require further investigation.

Novák defines endometriosis as the condition in which tissue resembling more or less perfectly the uterine mucous membrane occurs aberrantly in various locations in the pelvic cavity.

Endometriosis was first described to the medical profession in 1896 by Russell.

Sampson made his classical contribution in 1921 by ascribing the etiology of the condition to the regurgitation of the menstrual flow back through the Fallopian tubes, and bases these factors on:

1. Endometriosis can be demonstrated in cases of retroflexion with obstruction to the uterine or cervical canal.
2. The endometrial lesions are distributed in the dependent portion of the pelvis.
3. The tubes are usually patent.
4. Endometrium can be experimentally implanted on the peritoneum.

Myer and Novak among others believe that aberrant endometrium arises from the heteroplasia or the abnormal differentiation in the celomic epithelium from which all genital mucous membrane arises. You will recall that the Müllerian duct developed from an invagination of the primitive peritoneum or celomic epithelium.

Halban and Mestitz believe that the desquamating endometrial particles are transported by the lymph channels or the blood stream. It may be stated, however, that the histogenesis of all cases is probably not the same.

The analysis here presented covers a series of 569 cases of endometriosis. Of these, 112 patients were operated upon in the gynecologic department of the Presbyterian Hospital up to and including 1933 and reported by Dr. Edward Allen. To these have been added 457 patients with endometriosis who have been operated upon from the years 1934 to 1940, inclusive.

The cases of endometriosis selected for this study were private patients belonging to members of the obstetric and gynecologic department and were operated upon and have been followed for a period of from one to ten years. It has been possible to follow 291 of the 569 patients over this period of time and thus to give us pertinent data for this study.

*Presented at a meeting of the Cincinnati Obstetrical Society, October 16, 1941.

From the years 1934 to 1940 inclusive, there were 4,500 gynecologic operations. During 1934 there were 620 gynecologic operations, among which there were 52 cases of endometriosis, or an incidence of 8.4 per cent. During 1940, there were 713 gynecologic operations, among which there were 94 cases of endometriosis or an incidence of 13.1 per cent. This is not necessarily an indication that endometriosis occurs more frequently at the present time, but it may mean that at the present time we are better equipped to recognize the condition clinically. The incidence of endometriosis in the entire series of cases was 9.84 per cent.

Endometriosis occurs chiefly during the period of ovarian activity in a woman's life. The age limits in this series of cases extended from 16 to 78 years of age, 530 of them falling in the age group from 21 to 50 years of age. There were 235 patients in the age group from 31 to 40 years of age, far above the number in the other age groups.

Endometriosis itself or the conditions causing or responsible for its occurrence has a definite effect on fertility. There were 122 single patients and 262 patients who had one or more pregnancies in this series. One hundred sixty-eight of the patients were absolutely sterile, and 134 became pregnant and aborted, giving a relative sterility of 53 per cent.

Extensive endometriosis is rarely associated with pregnancy. When endometriosis and pregnancy are associated, abortion, premature labor, and extrauterine pregnancy may readily occur. In the presence of endometriosis interna and pregnancy, complications in labor are frequent. These may consist in rupture of the uterus, atony during cesarean section, or critical post-partum hemorrhage.

A number of the cases of endometriosis occurred some years after a pregnancy. The average time since the last pregnancy was 9.18 years. The average duration of the symptoms as recorded in the histories was 2.9 years. The interval between the last pregnancy and the onset of the symptoms, therefore, averaged 6.28 years. It is an interesting fact that practically all of these cases of endometriosis occurring some years following pregnancy were of the type known as endometriosis interna or adenomyosis, and occurred in the older age groups.

The symptoms elicited and the number of patients presenting each are found in Table I.

A detailed history is of the utmost aid in making a diagnosis of endometriosis. The order if not the frequency of occurrence of clinical symp-

TABLE I

SYMPTOMS	NUMBER OF PATIENTS
Dysmenorrhea	226
Dyspareunia	70
Backache	179
Bowel pain	25
Menorrhagia	300
Metrorrhagia	122
Abdominal pain	224
No symptoms	16

toms is acquired dysmenorrhea, backache often extending down the thighs, dyspareunia, increased or irregular bleeding, pelvic pain on jarring as in walking or car riding, low grade or acute bowel obstruction, and frequency of/or pain on urination.

One will find that there is no typical history in endometriosis. Typical dysmenorrhea need not be present. Dysmenorrhea when present is of the acquired type with some degree of progression. Endometriosis in many cases is responsible for pelvic pain even though the lesions are not firm enough to palpate either rectally or vaginally. Fixation of the uterosacral ligaments and the rectovaginal septum usually results in a pain of a bearing down nature and in a desire to defecate. These symptoms begin before menstruation is initiated and abate after the onset. In many cases a dull aching pain is present after the flow ceases. As the disease progresses the duration of the pain increases, so that in most severe cases patients may not be free from pain at any time. This pain is made definitely worse on exertion.

Dyspareunia is one of the most important symptoms found in endometriosis but is so seldom elicited in the history taken by the doctor. It is not uncommon for a patient to come to the doctor complaining of sterility or perhaps merely for a routine examination and the doctor might find extensive involvement of the pelvic organs in later proved endometriosis.

Bimanual pelvic examination is, of course, extremely important. On examination one may find the rather characteristic beading of the sacrouterine ligaments which may or may not be extremely tender to the touch. These are best palpated on rectovaginal examination. At times the patient is extremely difficult to examine because of the excruciating pain and discomfort. In this case, where pelvic pathology cannot be accurately determined, examination with the aid of ethylene and oxygen anesthesia or with intravenous sodium pentothal anesthesia is of great assistance. If it is at all possible to examine the patient without the aid of anesthesia, the diagnosis is usually more accurately made, because these affected areas are usually so painful. This is especially true immediately preceding a menstrual period.

The location of endometrial lesions found at operation and the frequency of occurrence of each are presented in Table II.

TABLE II

LOCATION OF LESIONS	FREQUENCY OF OCCURRENCE
Ovaries	345
Uterus	313
Cul-de-sac	191
Ligaments of the uterus	69
Sigmoid	8
Rectum	14
Tube	16
Abdomen	3
Bladder	3
Appendix	1

Superficial lesions varied from pin-point size to the size of about 5 mm. The superficial lesions frequently occur at the free border or the convex surface of the ovary, or the lateral surface of the ovary. The lesions are usually of a raspberry color, and there is usually an adherence to the contiguous structures. Nodular lesions are very frequently found along the junction of the sacrouterine ligaments, causing puckering and distortion of the peritoneum in this area. Occasionally small lesions are found scattered over the peritoneum that are visible only as star-shaped puckered areas. Some authors are of the opinion that these minute lesions are of but minor importance.

Endometrial cysts are usually no larger than a hen's egg. The chocolate cysts are frequently confused with follicle hematomas and with cystadenoma because of the hemorrhagic mixture.

The type of endometrium found on pathologic examination usually shows marked tendency toward hyperplasia. Of the 380 specimens of endometrium obtained in this group of cases 221 showed evidence of hyperplasia, 85 specimens exhibited the resting stage, and 74 showed the secretory phase of the cycle.

The associated pathologic conditions found accompanying many of the cases of endometriosis were numerous. Of these, the more frequent types were fibromyomas of uterus as found in 253 cases, outlet relaxation in 127 cases, retroversion of the uterus in 81 cases, and cervical erosion and cervicitis in 75 and 37 instances, respectively. There were four instances of carcinoma of the uterus associated with endometriosis.

The clinical diagnosis of endometrial lesions is frequently missed because of the multiplicity of associated pathologic lesions of the uterus and ovary which may themselves account for the greater part of the patient's symptomatology. Some of those symptoms mentioned should, however, direct attention to endometriosis even in the presence of other pathologic conditions.

The operations performed in this group of patients are shown in Table III.

TABLE III

OPERATIONS	INCIDENCE AMONG PATIENTS
Laparotomy	160
Vaginal	246
Laparotomy and vaginal	82
Webster round ligament shortening	52
Appendectomy	111
Presacral sympathectomy	5
Vaginal hysterectomy	225
Cauterization of transplants	71
Resection of the ovaries	72
Resection of transplants	80
Oophorectomy	233
Salpingectomy	230
Abdominal hysterectomy	134
Defundectomy	4
Myomectomy	23
Vaginal plastic	107
Dilatation and curettement	135

The policy followed in this clinic in the treatment of endometriosis is that of the conservative procedure. It is realized that irradiation therapy will usually relieve the symptoms, but it is felt that conservative operations are the procedures of choice. The patient can always have irradiation at a later date if it is deemed advisable subsequently to sacrifice the ovarian function. The fine cautery point helps greatly where dissection is impossible. Many times the utmost care is taken in removing the most minute spot of transplant with the electric cautery.

It is often necessary to remove one-third or even one-half an ovary in order to preserve some ovarian tissue. Surprisingly few patients with less severe endometriosis have had to be re-operated upon. Unfortunately too many women present themselves only after the lesions are very far advanced.

Constrictions of the cervix as well as retrodisplacements should be corrected wherever possible, keeping in mind the possible etiology of the condition.

There are reports in the literature of cases of endometriosis in which there has been spontaneous disappearance of massive implants following conservative operations in the pelvis.

- The value of presacral sympathectomy is seriously questioned by many authors. Endometriosis is localized to areas of the peritoneum not innervated through the presacral plexus, but through the spinal nerves. It is therefore impossible to perform the necessary neurectomy. It is possible that regression and ultimate disappearance of the lesions may take place, although it is uncertain whether or not the sympathectomy had anything to do with the regression.

The results, based on a follow-up of 291 cases of endometriosis post-operatively over a period of one to ten years, are shown in Table IV.

TABLE IV

RESULTS	
Average morbidity	1.16 days
Average days in bed	9.9 days
Mortality	0
Completely relieved	257 patients
Subsequent pregnancies	19 patients
Dysmenorrhea	7 patients
Dyspareunia	5 patients
Backache	9 patients
Bowel pain	8 patients
Menorrhagia	16 patients
Abdominal pain	2 patients

Turunen reported on 200 cases of external endometriosis in which radical operations were performed in only 22 per cent. Of the previously sterile women 31.7 per cent became pregnant after operation.

SUMMARY

1. The etiology of endometriosis is still an unsolved problem.
2. Incidence of endometriosis was 10 per cent in 4,500 gynecologic surgical cases.

3. Age incidence varied from 16 to 78, being greatest in the childbearing years.
4. There was a relative sterility of 53 per cent in this series.
5. Dysmenorrhea, menorrhagia, backache, dyspareunia, abdominal pain are the important symptoms.
6. Fibroids, retroversion, endocervicitis, outlet relaxation are the frequent associated pathology.
7. Location of the lesions is most frequently in the uterus, cul-de-sac, and ovaries.
8. Ovarian function was retained in 503 of 569 patients operated upon.
9. A total of 88.3 per cent of the patients remained symptom-free post-operatively.
10. There were 19 pregnancies subsequent to operation.

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2404 AUBURN AVENUE

Mayer, Victor, and Templeton, Fred. G.: *Inguinal Ectopia of the Ovary and Fallopian Tube*, *Arch. Surg.* 43: 397, 1941.

A swelling in the right inguinal region extending into the right large labium was first noticed in a girl when four months old. At the age of eight months this swelling did not seem larger, but there was difficulty in reposition. A month later the swelling recurred, was tender, and associated with vomiting. Operation seemed required. In the hernial sac were found the deeply cyanotic and slightly edematous right ovary and tube, which promptly attained normal color after being freed, and were replaced in the abdominal cavity. Recovery was uneventful.

The authors bring a complete list of recorded cases which they analyze particularly in regard to etiology, diagnosis, and treatment.

HUGO EHRENFEST.

PARATHYROID EXTRACT IN PRE-ECLAMPTIC TOXEMIA*

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THE presence of tetany in pregnancy and the puerperium was recognized and reported as early as 1830 by Dance and Steinheil¹ and in 1854 by Trousseau.² Erdheim³ noted that tetany appeared earlier, was more severe, and abortion and death occurred sooner in parathyroidectomized pregnant animals than in the nonpregnant. Also it has been observed that in animals with chronic parathyroid insufficiency following extirpation of the thyroidparathyroid glands, gestation is very likely to initiate tetanic convulsions. Thyroparathyroidectomized dogs given cod liver oil until symptoms of tetany disappeared developed tetany during pregnancy, lactation, and estrus.⁴

Sietz and Thierry⁵ noted symptoms of tetany in their obstetric patients, and tested the galvanic irritability of motor nerves during pregnancy and found it increased in the last month of gestation in 80 per cent of the 70 healthy women examined and a still further increase of nervous irritability was found at the time of delivery. Kelner⁶ noted positive findings in 75 per cent of his cases in the latter half of pregnancy as well as during the first ten days of the puerperium. Richardson⁷ reported that fully 75 per cent of all pregnant women suffer from some degree of tetany.

Symptoms of calcium deficiency during pregnancy appear usually in the middle trimester and increase in severity in the last trimester. More often obese patients, or those who have gained excessively, manifest symptoms of tetany. One reason for greater calcium deficiency in the obese is the fact that calcium combines with the neutral fat in the cells to form lipoids, in which form it is transported to its natural depots in the body. The most common symptom is spasm of the calf muscles. Other symptoms noticed which correspond to parathyroid insufficiency in patients following damage to or removal of the parathyroids in goiter operations are numbness and tingling of extremities, tightness in neck and chest, disturbance in swallowing, fatigue, and insomnia. Such patients are usually irritable and extremely nervous. They tire easily and may complain of cramps in the back and hips and wonder if the cause is not rheumatism. Ultraviolet light or vitamin D in addition to calcium has repeatedly relieved the hip and backache of many of my patients manifesting these symptoms. This beneficial effect I attribute to an increased assimilation of calcium.

Estimations of blood calcium during pregnancy vary. Bogert,⁸ Feinberg,⁹ and Davis¹⁰ find only slight variation during pregnancy. Widdows,¹¹ however, noted a decided reduction in the blood calcium

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The Eli Lilly Co. furnished the parathyroid extract for this study for which the author wishes to express his thanks.

level of women during the last two months of normal gestation. He found that serum calcium returned to normal after labor.

In our office, serum calcium estimations on obstetric patients in the last trimester have given a normal figure of 10 to 12 mg. in 85 per cent of those tested and a slightly lower figure of 8 to 9 mg. in the other 15 per cent.

Clinical symptoms of calcium and parathyroid deficiency with a normal total serum calcium have been reported. The body maintains the serum calcium at a normal level while withdrawing calcium from tissue reserves, thus giving rise to paresthesia and muscle cramps.

Maternal tetany occurs in the last trimester of pregnancy, this being the same period during which eclampsia or pre-eclamptic toxemia most often develops.

In a study of four patients having parathyroid tetany following goiter operations, I¹² found that two of these patients developed tetany only during pregnancy.

Mitchell,¹³ in 1910, advanced the theory of calcium deficiency as the exciting cause of eclampsia. Perpere¹⁴ (quoted by Lopez) reported five cases of eclampsia in which parathyroid extract produced a diuresis with the disappearance of edema.

Richardson⁷ reported two patients with pre-eclampsia, with blood pressures of 130 and 160 with a two-plus albuminuria and moderate visual and nervous symptoms, who become albumin free and showed complete symptomatic recovery in three to five days with administration of parathormone intramuscularly together with viosterol and calcium gluconate by mouth.

PERSONAL OBSERVATIONS

This is a clinical report of 1,000 pregnancies among which there were 88 cases having during the last trimester a systolic blood pressure of at least 140 and a diastolic blood pressure of 90. The highest figure was 185 over 110.

Thirty-four patients had a pressure above 150 over 100. In this group of 34 patients all had definite toxemia symptoms with varying degrees of ankle edema, fatigue, headache, epigastric distress, and albuminuria. The group with blood pressures ranging between 140 and 150 had no toxemia symptoms other than slight ankle edema and traces of albumin.

Along with the elevation of blood pressure, edema and excessive weight were symptoms of tetany, such as fatigue, irritability, numbness and tingling of the hands and feet, muscle cramps, insomnia, and weakness. The blood pressure in 86 cases was normal in early pregnancy and returned to normal after delivery. Two patients had chronic glomerular nephritis with elevation of blood pressure. One of these patients delivered a stillbirth at six months and the other a normal full-term baby. Parathyroid extract was used but found to be of no value in reducing the blood pressure due to nephritis. It did, however, lessen ankle edema.

It is not the purpose of this paper to discuss the pathogenesis or etiology of pre-eclamptic toxemia.

Because of the associated calcium deficiency symptoms in this group of pre-eclamptic toxemias, parathyroid extract,* as prepared by Collip,¹⁵ was used in 1 c.c. doses to elevate serum calcium. In every case the extract produced diuresis, lowered blood pressure, lessened ankle edema, and promoted weight loss. Whether the parathyroid extract benefited the patient by a detoxification action, by an effect on blood calcium and phosphorus, or by a diuretic action is not determined.

Edema or water retention in tissues is a typical finding in pre-eclamptic toxemia. Bayliss¹⁶ showed that the calcium ion decreases cell permeability and then tends to limit exudation and transudation.

According to Hamburger,¹⁷ the ratio of calcium, sodium, and potassium ions in a perfusing fluid is the determining factor in the formation of edema. It is evident that salt should be restricted and baking soda, which is sometimes used for heartburn, should be avoided if edema is present. The calcium ions tend to raise the resistance of the capillaries to permeation and at the same time act as a capillary stimulant, while the sodium and potassium ions on the other hand tend to increase the permeability of the capillary walls and favor exudation. Blum¹⁸ believes that the administration of calcium reduces the sodium content of the blood and prevents the migration of this ion into the tissues.

CASE REPORTS

CASE 1.—Mrs. A., aged twenty-eight years, a primipara, whose average weight was 165 to 170 pounds, consulted me when six and one-half months pregnant. Her blood pressure was 135 over 95 and there was moderate ankle edema present. At the eighth month her blood pressure was 150 over 95 and the ankle edema had increased. Her urinary output was 1,500 c.c. in twenty-four hours, and there was a definite trace of albumin.

The following week her pressure was 165 over 100; weight 192, and she had a dull headache and scotoma. The edema was more marked. One cubic centimeter of parathyroid extract was given, the blood pressure continued to rise to 175 over 100 and the weight was 190; the headache was less. Three days later she was again given parathyroid extract, and at the following visit four days later her edema was less, she had no headache and there was less swelling of the eyes, although the pressure was 185 over 100 and her weight 188. She was given another cubic centimeter of parathyroid extract. Three days later her pressure was 165 over 100 and her weight in the last twelve days had dropped from 192 to 181. Her pressure was now 168 over 100.

She continued to feel better and for the next fourteen days her pressure gradually dropped to 155 over 100, and her eye symptoms disappeared. The albumin in the urine was recorded as three-plus on the two office calls when the blood pressure was the highest. This gradually decreased as the pressure decreased until it was only a trace on

*Each cubic centimeter represents 100 units.

the day the blood pressure was 155 over 100. She had a normal delivery and an uneventful puerperium.

CASE 2.—Mrs. C., aged 22 years, consulted me when three months pregnant. Her blood pressure was 110 over 70. Her weight was 211 pounds and her average weight had been 185. Laboratory findings showed a mild anemia and negative urine. Her basal metabolic rate was minus 10 per cent. The patient was nervous as manifested by bitten nails. The distribution of obesity was of the hypoovarian type. The patient was given thyroid, iron, and ABDG capsules.

Early in the fifth month of pregnancy her blood pressure was 160 over 95. She was given parathyroid extract, a reducing diet low in sodium chloride, and was advised to rest two hours in the afternoon. She was also given $1\frac{1}{2}$ gr. of phenobarbital tablets for sleep at night. Her pressure dropped to 140 over 80 in one week and to 120 over 80 in another week. In the sixth month the patient suddenly gained 7 pounds in two weeks and her blood pressure rose from 120 over 80 to 155 over 85. One cubic centimeter of parathyroid extract again brought the blood pressure down to 135 over 80 in one week.

In the remaining two months of pregnancy on careful dieting, the pressure went above 140 over 90 only twice and parathyroid extract brought it to 130 over 80 each time. The patient gained 50 pounds during pregnancy and delivered a normal healthy male infant weighing 8 pounds.

Twelve other patients with blood pressures ranging from 140 to 178 systolic and 90 to 110 diastolic had considerable edema of the ankles. These were given three to four injections of 1 c.c. of parathyroid extract and all but two showed lessened edema and a decrease in blood pressure in one to two weeks. Clinical improvement appeared before the decrease in the blood pressure; the diastolic pressure was the last to show improvement.

Three patients showed very little improvement in their ankle edema or in reduction of their blood pressure from the use of parathyroid extract. Five patients manifesting ankle edema but having normal blood pressures were given parathyroid extract and a definite benefit was obtained.

In analyzing this group of toxemic patients, I find that the average gain in weight was 28.5 pounds. The greatest gain in weight was 50 pounds in a single pregnancy and 49 pounds in a twin pregnancy. All babies were full-term normal infants except three. One twin born by cesarean section developed spastic quadriplegia. One baby died forty-eight hours after delivery due to a congenital heart lesion. One baby whose mother had nephritis with hypertension was delivered a stillbirth at six months.

Each patient after the sixteenth week received 15 gr. of dicalcium phosphate before each meal unless she drank a quart of skimmed milk daily. There is better absorption of calcium from the intestinal tract when given without food. In the winter months when no sunshine was available ABDG capsules were given. The patient was encouraged to drink plenty of water and to avoid fats and excess carbohydrate foods.

The action of the parathyroid hormone and that of vitamin D are probably different in that the former increases serum calcium by the withdrawal of the element from bone and tissue reserves¹⁹ and the lat-

ter increases the absorption of calcium from the gastrointestinal tract.²⁰ Undoubtedly a lack of calcium or vitamin D during pregnancy throws an added burden on the parathyroid glands. For this reason it seems reasonable that all women during pregnancy and lactation should be given a calcium rich diet, and to insure absorption and utilization of the calcium some form of vitamin D should be added.

SUMMARY

A brief review of the literature dealing with the incidence of tetany in pregnancy and its relation to pre-eclamptic toxemia is given.

Calcium and vitamin D were found effective in relieving the symptoms of maternal tetany. Parathyroid extract was found to be of value in reducing edema and relieving the symptoms of pre-eclamptic toxemia. Clinical improvement preceded the fall in blood pressure. The systolic and diastolic pressures dropped in all patients but did not return to normal until after delivery. There were no cases of eclampsia in this series and no maternal deaths. I refer to deaths because toxemia of pregnancy causes approximately 25 per cent of maternal deaths.²¹

In this series it was not found necessary to give intravenous glucose or hospitalize any of these pre-eclamptic patients. Foods rich in calcium, protein, and vitamin D were included in the diet. Additional rest with or without sedatives was used when indicated. Magnesium sulfate was not used orally to promote elimination nor was it necessary to restrict water.

Certainly one should not infer from this paper that parathyroid extract alone can relieve the symptoms in all cases of pre-eclamptic toxemia, but I believe it is a useful drug in the early cases and should be tried in a larger series of greater severity.

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PRIMARY BREECH BIRTH

EXPERIENCES IN 20,000 DELIVERIES

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PRIMARY breech presentation occurs with a fair constancy in any appreciable group of births. Since it has been thought, and with good reason, to constitute an additional hazard to the parturient, an appraisal of our own incidence, procedures, and maternal and fetal results seems of value. This analysis concerns 859 primary breech deliveries in a series of 20,000 deliveries occurring over four and one-half years at the Margaret Hague Maternity Hospital, an incidence of 4.3 per cent.

It is regrettable that the majority of statistics do not qualify breech presentations sufficiently to answer some of our perplexing questions. For instance, do figures include nonviable and premature babies (which are freely movable or "nonfixed" in utero) with full-term or "fixed" breeches? Is recognition given the difference in technical demands upon the operator which this distinction imposes? Are the maternal dangers and obvious effects upon the fetus recognized in fixed as compared to nonfixed, or premature breech births? What controls the choice of operative procedures? What are the factors complicating delivery, and how are they influenced by the parity of the patient?

Unless a particular analysis helps answer these questions, it is but a mass of meaningless figures. It is apparent that an essential step is to divide breech presentations into (1) "free" or "nonfixed breeches" occurring with nonviable and premature babies under 2,500 Gm. or under thirty-two weeks' gestation, and (2) "fixed breeches" occurring in patients approximately at term with average-sized babies, and with labor imminent or begun.

The *nonfixed breech* with a premature or nonviable baby presents little technical difficulty. It is capable of free and easy motion within the uterus. The majority deliver spontaneously and without trauma to the maternal soft parts. Inevitably, the fetal mortality must be high, due to fetal lack of development. In this series, including nonviable and neonatal premature deaths, it was 46.7 per cent. Where prematurity is associated with multiple pregnancy, there is a sharp rise in fetal death rate.

Little maternal danger exists from the nonfixed breech with premature fetus with respect to delivery technique. There is considerable hazard, however, from certain conditions which initiate premature labor, espe-

ially nephritis, pregnancy toxemia, abruption of the placenta, and placenta previa. Thus the maternal problem in this group is the management of the *complicating factor* rather than the fact of breech presentation.

When we consider the *fixed breech*, the fetus of average size, not easily dislodged from its presentation at or near term, the entire picture changes. The fetus is now capable of surviving under ordinary extra-uterine conditions, but presentation by the breech means increased likelihood of injury. Trauma to an unmolded aftercoming head, the danger of nuchal extension of arms, and cervical retraction with arrest of the fetal head, imperil the vigorous fetus. Impaction is to be feared in multiple pregnancy at term. Undue pressure on the fetal body may produce adrenal apoplexy, or injure the spine or viscera. Consequently, the fixed fetus at term is endangered but in different ways than is the premature, nonfixed fetus. Here the total of full-term stillbirths and neonatal deaths from all causes was 76, or 11.2 per cent.

The *maternal hazards* in this group are increased, for not only may the same complications occur as noted with premature parturitions, but there are added dangers dependent on the mechanics of delivery. Arrest of the fetal head after expulsion of the trunk is common. Misapplication of force or improper technique may produce nuchal extension of arms or severe lacerations of the cervix. The vaginal canal and perineum are commonly lacerated, and extension of episiotomy wounds frequent. Injudicious application of forceps to the aftercoming head jeopardizes the baby and may severely traumatize maternal tissue.

The *parity of the patient* is important, for although in our experience full-term fetal mortality in primiparas and multiparas does not vary greatly, the maternal threat is much greater to the primipara. The experienced operator recognizes in a primiparous fixed full-term breech a problem which may tax his judgment and technique to the utmost.

We are not of the opinion that the term "assisted breech delivery" is a good one to describe an elective procedure to assist the normal expulsive forces. There exists confusion as to how far *assisting* may go before it becomes *operative interference*. It would be acceptable if it were standardized to describe guiding procedures after expulsion of the fetus to the umbilicus. Forceps to the low aftercoming head to flex it and control its passage over the perineum is less hazardous than accepted manual procedures, but certainly more dangerous in higher applications. But in this review, lack of precision in recording the level at which the aftercoming head forceps were applied makes attempt to classify them on this basis valueless. All operative procedures are therefore grouped together.

Of the 859 breech cases, 195 were delivered by operative procedures. In 168 instances, forceps were applied to the aftercoming head, an

incidence of about 20 per cent. In our opinion, this could be increased with benefit to both mother and baby. It is of significance that in most of the 51 full-term fetal deaths, forceps were not used, or used after other methods failed. Three cases of adrenal apoplexy causing fetal death were ascribed to body-mauling in an attempt to deliver the head without forceps.

There were 20 cesarean sections in this group, or 2.3 per cent. This approximates the general cesarean section incidence in the hospital. They were for a variety of indications and mainly performed at full term. It is our personal belief that many of the thirty-three primiparous

TABLE I

	TOTAL	FULL TERM	PREMATURE AND NONVIABLE	STILLBORN FULL TERM	(UNCORRECTED) PREMATURES AND NONVIABLE	NEONATAL DEATHS	
						FULL TERM	PREMATURES
Primiparas	508	404	104	33—8.1%	29—28.0%	17	6
Multiparas	351	271	80	18—6.6%	40—50.0%	8	11
Totals	859	675	184	51—7.5%	69—37.5%	25	17
Total full-term stillbirths and neonatal deaths					76, or 11.2 per cent		
Total premature stillbirths and neonatal deaths					86, or 46.7 per cent		

TABLE II. MULTIPLE PREGNANCY

		ONE BREECH	MORTAL	BOTH BREECH	MORTAL
Breech, twins	96	60	0	18 sets	0
Breech, triplet	1	1	0		

TABLE III. OPERATIVE DELIVERY

Forceps to aftercoming head	168, or 19.5%
Cesarean section	20, or 2.3%
Craniotomy	7
No maternal deaths	

term stillbirths (8.1 per cent of all full-term primiparous breech births) could have been averted by increasing the operative incidence with more frequent judicious performance of cesarean section. Since comparable figures of 18 full-term stillbirths in multiparas (6.6 per cent) were shown for this series, resorting to cesarean section *too readily* for all breech presentations would be neither sound nor safe. Obviously section is *necessary* in certain cases of breech presentation complicated by placenta previa, abruption of the placenta, progressive toxemia of pregnancy, and prolapse of the cord through an undilated cervix. It is *often* advisable when nephritic toxemia, chronic hypertension, and chronic heart disease complicate the picture. Especially if one considers infertility, age, and a desired future sterility, we believe that we have been overconservative. But as at other times, the election of this major abdominal operation must depend upon the exercise of good judgment after thorough consideration of all relevant data.

Craniotomy was performed seven times upon the aftercoming head. Three of these were hydrocephalies. In all seven cases, the fetus had

already died. Craniotomy on the aftercoming head is not lightly to be undertaken. Obviously it is a "way out" of an already bad situation. One of our cases developed a vesicovaginal fistula requiring subsequent correction.

The primiparous breech patient presents *factors complicating delivery* which separate here from the multipara. As might be expected, this study showed her to be a more likely candidate for toxemia of pregnancy, and more apt to lose the baby if the cord prolapsed.

Placenta previa is a common complication in multiparas, 2.3 per cent as compared to 0.4 per cent in primiparas, and the degenerative diseases and their accompaniments, as nephritis with abruption of the placenta, are more often encountered. These are best noted in Table IV which sets forth some of these factors complicating breech births. It may be observed that the nonfixed premature breech is encountered more often in the multipara, but is of significance largely by reason of the complicating factor.

TABLE IV. COMPLICATIONS, FULL TERM.

	PRIMIP- ARAS	FETAL DEATHS	MULTIP- ARAS	FETAL DEATHS	TOTALS	TOTAL FETAL DEATHS
Prolapsed cord	6	3	6	0	12	3
Prolapsed arm	0	0	1	0	1	0
Heart disease	1	0	2	0	3	0
Chronic nephritis	0	0	1	0	1	0
Pregnancy toxemia	8	2	1	1	9	3
Abruptio placentae	0	0	1	1	1	1
Placenta previa	0	0	6	1	6	1
Pyelitis	1	0	0	0	1	0
Spina bifida	4	2	2	2	6	4
Anencephalus (monsters)	1	1	2	2	3	3
Premature stillborns; placenta previa, 4; prolapsed cord, 4; eclampsia, 1; abruptio placentae, 1; nuchal cervical retraction, 1.						

Prudent and rational *management of the full-term fixed breech* depends therefore on the careful observation and evaluation of all mechanical and complicating factors. The parity of the patient may be important, as in prolapsed cord in a primipara with living baby. The age may be all important, as in elderly primiparas or in those of known relative infertility, making inadequate progress in labor. It is morally wrong and socially unjust to render pregnancy and parturition fruitless for such women by ill-advised overconservatism. The condition of the cervix and parity in abruption of the placenta may determine procedure. Obviously, the primipara not in labor presents a problem requiring vastly differing treatment from the multipara in labor with well-dilated cervix and with ample pelvis. The presence of a monstrosity may alter one's course. Such considerations have more bearing upon the course of labor, management and results to mother and fetus than pelvic capacity or architecture.

Post-partum complications are influenced somewhat by parity and age. Severe lacerations were noted in our series more in primiparas, while post-partum hemorrhage, adherent placenta, cardiac complications and renal impairment were observed with greater frequency in multiparas, especially elderly. This is in accord with common obstetric knowledge, but upon its application depends the lowering of risks to mother and fetus. There were no severely septic cases, but endometritis with foul lochia was noted more often in elderly multiparas. When this occurred it almost invariably followed manual removal of an adherent placenta. Breech presentation per se does not seem to increase the hazards from medical complications unless dystocia develops and operative termination of labor ensues.

Certain complications have a direct bearing upon the fetus and *fetal mortality*. Thus, of 16 cases with prolapsed cord, 7 babies died. Abnormal fetation accounted for 9 fetal deaths, and extension of the arms with arrest of the head at the inlet undoubtedly caused fatal delay and trauma in the majority of full-term stillbirths, although this is difficult to show statistically. Fractures of the clavicle are not infrequent^s but unimportant if properly treated. One humerus was fractured. There were no cases of Erb's paralysis noted immediately or recorded in clinic follow-up. There was one case of cerebral hemorrhage with arrest in mental development.

There was no maternal mortality in these 859 patients.

SUMMARY

In the consideration of the fact, management, and outcome of primary breech presentations, the size and viability of the fetus, pelvic architecture, coexisting complications of pregnancy, pre-existing or coexistent disease, influences of age and fertility, and the parity of the patient have reciprocal rather than individual significance.

In this study of 859 primary breech births with an incidence of 4.3 per cent in 20,000 deliveries, attention is directed to the operation of such reciprocally important factors governing fetal and maternal safety. In this manner the more important aspect of *preventable* fetal and maternal morbidity and mortality may be contrasted with *gross* figures.

CHONDRODYSTROPHIC DWARFISM IN PREGNANCY

REPORT OF TWO CASES

H. C. SPALDING, M.D., RICHMOND, VA.

(From Department of Obstetrics, Medical College of Virginia)

THE subject of dwarfism has been an age-old excitant of human curiosity. For this, if no other reason, it seems strange that so little space in medical literature has been devoted to this subject.

Guggisburg¹ distinguishes between proportionate and unproportionate dwarfism or nanosoma, ehondrodystrophic dwarfs being in the latter group. The older editions of Williams² give a fuller description of this anomaly than any other American reference available. The case described by Williams was a 27-year-old dwarf, 123 cm. tall, who died after cesarean section. Balasquide,³ in 1935, reported a case of dwarfism in a Puerto Rican. To judge by the photograph, his dwarf did not appear quite as unproportionate as did my case reported below. The most fertile source of references to chondrodystrophic nanism was found in Kaufman's text on *Pathology*.⁴ He states that this condition may appear in either intrauterine life or sometime after birth, and that the deviation from normal is chiefly in the shortness of the long bones. The soft tissues are normally developed so that the redundant skin hangs in folds as would a dress made with too much cloth. These changes are due to incomplete growth of the cartilage and early cessation of enchondral ossification. When observed at birth, Kaufman states, this condition has been erroneously called fetal rickets and should be called chondrodystrophia fetalis. He adds that nothing is known of its etiology or therapy, but concerning the incidence and prognosis a few patients have been reported living past thirty and one even to the age of eighty. The majority, however, die in the first few weeks of life. None is taller than 140 cm. Some may be of high intelligence.

Since our texts quote only the foreign example (Breus and Kolisko,⁵ 1900) of chondrodystrophy complicating pregnancy, I am moved to add two patients treated on the wards of the Medical College of Virginia.

CASE REPORTS

CASE 1.—L. T. (Hospital No. 17,876), 22-year-old, unmarried, colored, primigravida, was referred to St. Philip Hospital Jan. 11, 1934, by Dr. C. R. Robins of Hopewell, Virginia, because of failure of progress in a term labor of thirteen hours. She was one of seven sisters, one of whom had died of tuberculousis, the remaining five being normal and healthy. She had been told she was born with deformed extremities. An attack of measles prevented her having an entirely negative past history. Menses had begun at the age of thirteen and were normal. Her pregnancy had been uneventful until the spontaneous rupture of her membranes and the onset of labor.

Examination revealed a somewhat fat girl, obviously pregnant and in labor. There was a very unusual conformation of face and extremities. This unusualness can better be appreciated from her pictures than from description. She was 119 cm. tall and after delivery weighed 43.2 kg. A macroglossia was noted. Her fundus uteri measured 40 cm. above the symphysis pubis. A single fetus lay in the L.O.T. position with a heart rate of 164 per minute in the L.L.Q. Vaginal examination revealed prominent ischial spines, a partially effaced, soft cervix 2 cm. dilated, with the vertex floating. Pelvimetry was as follows: Inter-spinous 22 cm., intercrystal 21 cm., intertrochanteric 34 cm., Baudelocque 14 cm., right oblique 16 cm., left oblique 18 cm., depth of symphysis 3 cm., intertuberous 9.5 cm., anterior sagittal 7 cm., posterior sagittal 9.5 cm., anteroposterior 11 cm., diagonal conjugate 7.5 cm.

A low cervical double flap cesarean section under spinal anesthesia (125 mg. novocain crystals) resulted in the delivery of an apparently normal, 3,540 Gm. living male.

A temperature high of 102° F. was noted about twenty-four hours after operation. Her puerperium was otherwise satisfactory. In order to make further studies, the patient's hospital stay was prolonged to seventeen days. All additional studies were essentially negative. Tele-roentgenograms showed one-half internal diameter of the chest to be 11.1 cm. with the transverse diameter of the heart 10 cm. An electrocardiogram was normal, except that on Lead III there was evidence of left axis deviation. The basal metabolic rate was plus 23 per cent. Blood and urine remained negative.

The mother and baby were discharged in good condition Jan. 28, 1934. On April 3, 1937, she reported that both had been well except for progressive weakness in the baby. Inspection revealed that he, three years and two months old, was showing unmistakable evidence of chondrodystrophism. Roentgenogram report of her long bones at this visit stated: "Examination of the right humerus showed it to measure 16 cm. in length, as measured on the film. There was marked irregularity of the contour and apparently no head in articulation with the glenoid cavity. The upper radius and ulna were included on the film and showed the same general shortening with some deformity."

"A film of the distal left femur, all of the tibia and fibula and ankle joint, showed considerable deformity of all the bones mentioned. There was marked external bowing which apparently had its origin at the condyle of the tibia, as the medial condyle was much flattened as though there had been a marked disturbance of the epiphyseal growth on the medial side. The tibia measured 26 cm. in its longest line. The fibula was likewise bowed but did not show marked disturbance of growth at the epiphyseal center. The bones about the ankle joint were apparently fused especially in the region of the talus and cuneiform, and probably the navicular. This picture is comparable with achondroplasia (chondrodystrophia fetalis)."

CASE 2.—I. L. (Hospital No. 40,911), 30-year-old, single, colored primigravida, was referred to St. Philip Hospital May 13, 1937, by Dr. Clarence Campbell of Sparta, Virginia, because of term labor of twenty-one hours' duration without progress. Both parents and all nine sisters and brothers were living and in good health. No other dwarfism occurred in her family. Her menses had begun at fifteen

*F. B. Mandeville, M.D., Roentgenologist, Medical College of Virginia Hospitals.

years of age and were normal except for slight dysmenorrhea. Past history revealed measles, mumps, chicken pox, pertussis, typhoid fever, arthritis, and tonsillitis for which she had a tonsillectomy and adenoidectomy. Her pregnancy was uneventful except for swelling of her feet and ankles for the last three months. Labor was said to have begun twenty-one hours prior to coming to hospital, and on admission good contractions were occurring every five minutes.

Examination revealed a rather intelligent unproportionate dwarf 132 cm. tall, weighing 47.6 kg., with a large head, saddle nose, prominent forehead and arms longer than forearms; legs were quite short in relation to trunk. Fundus uteri measured 31 cm., and the fetal head overrode the maternal symphysis. Her pelvic measurements were: interspinous 22 cm., intereristal 23 cm., intertrochanteric 31 cm., Baudelocque 17 cm., obliques 19 cm. and 19.5 cm., pubic arch 35°, depth of symphysis 5 cm., intertuberous 6 cm., anterior sagittal 4 cm., posterior sagittal 6 cm., anteroposterior 5.5 cm., diagonal conjugate 9.5 cm.

Dr. C. L. Riley, now of Winchester, Virginia, delivered by cesarean section a 2,820 Gm., apparently normal, living male child. As with the first case, the convalescence was normal. Blood chemistry, except for calcium of 7.2 mg. per 100 c.c., was normal. Basal metabolic rate was plus 24 per cent fourteen days after operation. All the long bones were short but presented none of the white lines or rickets, no periosteal elevations, and showed satisfactory density.

Mother and baby were discharged April 1, 1937, in good condition.

SUMMARY AND COMMENT

1. Two cases of chondrodystrophie nanism are presented.
2. The first case, more marked than the second, measuring 119 cm., was 4 cm. shorter than the European example cited by Williams.
3. Spinal anesthesia was used because it was thought there would be insufficient cooperation for local infiltration.
4. Blood calcium of 7.2 mg. per 100 c.c. in the second case (this observation was not made in the first) is quite low. Only similar determinations in other cases of true chondrodystrophism can evaluate this finding.
5. Within the extent of our researches, chondrodystrophie dwarfs are entirely normal people except for the results of faulty cartilage formation and ossification and in one case a low blood calcium.
6. The child of one dwarf showed chondrodystrophy at the age of three.

REFERENCES

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2. Stander, H. J.: *Williams' Obstetrics*, ed. 7, New York and London, D. Appleton-Century Co., pp. 993-996.
3. Balasquide, L. A.: *AM. J. OBST. & GYN.* 30: 430, 1935.
4. Kaufman, Edward: *Pathology* (Translated by Stanley P. Reimann, M.D., 1929), Philadelphia, P. Blakiston's Sons & Co. 2: pp. 1169-1179.
5. Breus, Carl, and Koliško, Alexander: *Die Pathologischen Beckenformen*, 1900, 1: *Zwergbecken*, pp. 259-366, Leipzig und Wien, F. Deuticke.
6. Gould and Pyle: *Anomalies and Curiosities of Medicine*, Philadelphia and London, 1896, W. B. Saunders Co.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 14, 1941

The following paper was presented:

A Combined Study of the Causes of Fetal and Neonatal Mortality from the Sloane Hospital for Women and the New York Lying-in Hospital. Dr. D. Anthony D'Esopo (by invitation) and Dr. Andrew A. Marchetti. (To be published in a later issue.)

MEETING OF NOVEMBER 11, 1941

The following papers were presented:

Vaginal Hysterectomy With Pryor Clamps. Dr. Walter T. Dannreuther, New York, N. Y.

Studies in Gross Pelvic Anatomy and Their Application to Gynecologic Surgery. Dr. Arthur H. Curtis, Evanston, Ill. (by invitation).

MEETING OF DECEMBER 9, 1941

The following papers were read:

Infectious Lesions about the External Genitals. By Dr. Mortimer D. Speiser. (For original article, see page 681.)

Observations on Hemolytic Streptococcus Infections Following Delivery and Abortion Since the Advent of Sulfanilamide. By Dr. William E. Studdiford. (For original article, see page 619.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 1, 1941

The following papers were presented:

Résumé From a Recent Meeting of the American Gynecological Society. Dr. S. A. Chalfant.

Ovarian Tumors Complicating Pregnancy. Dr. C. R. Nucci.

Report From the Clinical Congress of the American College of Surgeons. Dr. D. Katz.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Puerperium

Koller, Th., and Umbricht, W.: The Alteration of the Blood Picture During Labor and Its Prognostic Value for Puerperal Morbidity After Spontaneous Child-birth, *Zentralbl. f. Gynäk.* 64: 1454, 1940.

The authors studied changes in the leucocyte count and its distribution in 630 normal deliveries. They found, especially evident during prolonged labors, that there was a characteristic rise and fall of leucocytosis as well as typical changes in the proportions of the various types of white cells. From the amount of excess leucocytosis and particularly from the percentage of staff cells, when over 25 per cent, the authors felt they were able to forecast with accuracy the onset of puerperal morbidity.

R. J. WEISSMAN.

Koller, Th., and Bietenholz, Ad.: Blood Picture During Labor and Its Prognostic Significance for the Puerperium, *Zentralbl. f. Gynäk.* 64: 1763, 1940.

The authors compared the hematologic statistics of 798 spontaneous and 573 operative deliveries with reference to the staff cell percentage during labor and its relation to puerperal morbidity. They conclude that an increase over 25 per cent in staff cells, especially in association with fever, is prognostic of puerperal complications in over 50 per cent of cases. This increased staff cell count, when taken into consideration with the factors of elevation of temperature, elapsed time since rupture of membranes and counted uterine contractions, is valuable in foreseeing infectious or thrombotic complications. The authors also feel it may be a useful deciding factor when the question of cesarean section comes up, as well as for vaginal operative delivery. The staff count is also increased in fetal death during prolonged labor. No mention is made of the analgesia or anesthetics used nor of their possible effect upon the hemogram. Their conclusions are based on the study of statistics covering twelve years.

R. J. WEISSMAN.

Chesterman, John H., and Scandrett, Shirley: The Incidence of Hemolytic Streptococci in the Throats of Obstetric Nurses. Results of Treatment by Tonsillectomy and Sulfanilamide, *M. J. Australia* 2: 695, 1940.

Over a period of two and one-half years the authors studied the occurrence of hemolytic streptococci in the throats of the nursing staff. This study was made to determine (1) the incidence of the organism in the throats of nurses resident in the hospital; (2) the effect of the presence or absence of tonsils; and (3) what methods if any will eradicate the infection.

Their figures suggest that hemolytic streptococci will invade a throat with tonsillar tissue more easily than one without, and that once they have become established it is more difficult to dislodge them from the throat in the presence of tonsillar tissue.

The presence of tonsils increases the liability of infection, while the absence of tonsillar tissue renders the subject less susceptible to infection with hemolytic streptococci.

Treatment varied between local therapy, tonsillectomy, and sulfanilamide. The authors conclude that tonsillectomy has proved successful in eliminating hemolytic streptococci from the throats of 26 of the 29 nurses whose subsequent history is known, and that sulfanilamide therapy in adequate doses (7 mg. per cent in the blood for five days) is shown to be a valuable method when other measures fail.

WILLIAM BERMAN.

Gueniot, P.: Results Obtained by the Preventive Use of the Sulfamides During Labor. *Rev. franç. de gynéc. et d'obst.* 36: 27, 1941.

In a series of 1,235 labor cases, the author routinely administered sulfanilamide each day during the first week following labor. There was no mortality in this series and the morbidity was remarkable because of the mildness of the infections, the short duration of fever and the rapid disappearance of symptoms.

J. P. GREENHILL.

Benthin, W.: Combatting Septic Conditions With Prontosil, *Zentralbl. f. Gynäk.* 65: 484, 1941.

In evaluating the effect of sulfanilamide in septic conditions, the many factors influencing the course of the infection must always be borne in mind. The author considers a septic patient to be one with continuing rapid pulse and pyrexia in association with more or less chronic bacteriemia. One must not consider that a patient who has had but one chill is pyemic and that the administration of prontosil has cured her. A third of all pyemia has a purulent thrombophlebitis associated with it in a more or less marked lymphogenous process in which the prognosis is hardly better than in simple pyemia. Therefore pyemia and sepsis are not to be considered as synonymous, especially when some writers include the peritonitic complications under the latter heading. Bacteriologically pyemia is generally a mixed sepsis, a predominantly streptococcal infection.

In Benthin's 37 treated cases of sepsis with septicopyemia, the mortality was 43 per cent, most of these having chemotherapy initiated after many chills. Three patients who had from 18 to 87 chills with elevated temperature were saved, although, in these, mixed infection could not be ruled out. Of the remaining survivors only one had had more than one chill before general treatment had been initiated. The bacteriologic study of fatal cases of pyemia showed no predominant lethal effect attributable to either streptococcal, staphylococcal or mixed infections. In true sepsis, however, with a mortality of 45 per cent out of 56 puerperal and 36 post-abortion cases, the incidence of streptococcal infection for the series was 80 per cent, mostly hemolytic. In 42 streptococcal cases there were 24 deaths; 17 deaths occurred in 33 hemolytic infections.

In spite of mortality figures of 33 to 54 per cent in large series of cases of peritonitis, prontosil should be tried. Also for puerperal endometritis statistics are extremely difficult to evaluate especially with the borderline between endometritis and generalized infection often difficult to define. In 1,200 cases studied by Benthin, 388 untreated and 387 prontosil treated cases of mixed infection endometritis recovered. In the treated streptococcal cases only 8 deaths occurred in 420 cases. In 286 cases of nonhemolytic streptococcal endometritis there were 6 deaths.

Results in postabortion morbidity are also difficult to interpret, prognosis depending on many factors, the best outlook being in cases with infection confined to the

uterine cavity. In complicated febrile states the mortality now is 28.8 per cent, as against 47.5 per cent before chemotherapy.

The author cites the excellent results of other workers with prophylactic use of prontosil in septic conditions given in doses of 10 Gm. over four days. This is emphasized by a collection of 5,572 normal births and 42 cases of protracted abortion prophylactically treated with a fever-free incidence of 99.82 per cent. Where elevation of temperature occurred it was of short duration.

A group of 113 cases with streptococci in the vaginal secretions, prophylactically treated with prontosil, showed a brief puerperal morbidity incidence of 43 per cent. None were seriously ill. Sixteen of the above group had early rupture of membranes and only 2 of these were seriously ill. Other complications prophylactically treated without serious illness were 7 placenta previas, 10 multiple pregnancies, 67 cases of cephalopelvic disproportion, 5 transverse presentations, 11 manual deliveries of placenta and 18 cases of retained secundines. In 269 cases, pyclitis was treated with prontosil without mortality, but it must be remembered that three-fourths of these cases were due to *B. coli* or staphylococcus infection. The author's results in mastitis, phlebitis, and pyosalpingitis were not considered significant.

Those who expect prontosil to be as effective in septic conditions as quinine is in malaria will be disappointed. Individualization of the treatment and a great deal of clinical acumen are needed, as well as early application with sufficient dosage of the chemotherapeutic agent. Its use must not be discontinued too soon. No mention of the newer sulfa drugs is made in this review.

R. J. WEISSMAN.

Caffaratto, Tirsi Mario: Puerperal Thrombophlebitis, Ginecologia 17 (Series 2): 1, 1941.

Caffaratto reports on 71 cases of puerperal thrombophlebitis encountered among 42,827 deliveries and abortions. Seventy cases of thrombophlebitis developed in the puerperal period of 36,697 labors and one single case was found among 5,654 abortion patients.

The author reviews multiple theories of the pathogenesis of thrombophlebitis. He discusses in detail the changes in the vascular currents, the vascular tree changes, the blood changes found in thrombophlebitis, those following operations, those in the normal puerperium and the many infective factors.

In 50 of his 71 cases of puerperal thrombophlebitis he noted that this complication was associated in 9 instances with placenta previa, three times with postpartum hemorrhage, with 11 cases of toxemia of pregnancy, in 8 cases having associated cardiac disease, 2 times with concomitant diseases of the respiratory tract, 6 times with severe anemia, 7 times with related pelvic disease, and on 1 occasion in each of the following complications: ruptured uterus, full-term extrauterine pregnancy, hydramnios, and twin pregnancy.

Thirty-three of the 71 puerperal thrombophlebitis cases followed normal spontaneous delivery. This complication followed forceps delivery in 18 cases; external version in 7, embryotomy in 5, placental extraction in 2 cases; podalic extraction in one case; uterovaginal packing in 13 cases, cesarean section in 4, cervical incisions in 8, induced labor in 6, puerperal curettage in 3, postabortal curettage in 3 cases, and occurred during labor in one instance.

Thirty-seven were primiparas, 16 were secundiparas, while the remaining 12 had 3 or more previous confinements.

In 84 per cent of this series the thrombosis was on the left side, while in 32 per cent the condition was found to be bilateral. One-third of the patients noticed the first pain in Scarpa's triangle, another third in the calves of the legs and 11 per cent in the popliteal space. The pain persisted for one to ten days in 37.2 per cent

of the group, from ten to twenty days in 37.2 per cent, and twenty to thirty days in 17.6 per cent of the series.

Embolism followed thrombophlebitis in 6 cases, an incidence of 8.4 per cent of the thrombophlebitis group, and 0.01 per cent of the total puerperal cases. Three of these patients died.

The author concludes that puerperal thrombophlebitis is best treated by the usual preventive measures. For local treatment he recommends the Jäger-Fischer method. This consists primarily in an early application of an unctuous plaster mold. Nineteen patients were treated in this manner. He reports that the edema and pain leave nearly two weeks sooner with this method as contrasted to other types of local therapy.

The author lists a valuable and comprehensive bibliography of 508 references.

CLAIR E. FOLSOME.

Jacobi, Hans: Treatment of Febrile Postpartum Mastitis, *Deutsche med. Wchnschr.* 66: 734, 1940.

Various methods of treatment are discussed. Jacobi prefers the 6-meter short wave. The immediate relief of pain is outstanding. There appears to be no effect upon the quality of the mother's milk and in this series of cases no supplementary feeding was necessary for the infants as the lactation was actually increased. A large electrode is placed over the scapula of the affected side and a Schliephake electrode is placed over the affected breast at a distance of 1 to 1½ cm. Emphasis is placed on early diagnosis and treatment. The incidence of surgical intervention in this condition has been reduced from about 36 to 5.4 per cent.

R. J. WEISSMAN.

Arbogast, W., and Embacher, E. M.: Treatment of Puerperal Tetanus, *Zentralbl. f. Gynäk.* 64: 1650, 1940.

The high mortality of puerperal tetanus is well known. A 31-year-old woman who had some weeks previously aborted herself by means of a laminaria tent, had sharp bleeding shortly after taking a vaginal douche. Eight days later she experienced difficulty in moving the jaw and by the tenth day the jaws were firmly locked. Five grams of avertin were administered and 40 c.c. of spinal fluid were drawn off and replaced by 12,500 units of tetanus antitoxin. Vaginal examination revealed a uterine infection and with 4 more grams of avertin a total vaginal hysterectomy was done. In twenty days the patient received a total of 720,000 units of antitoxin and 128 grams of avertin in 18 doses. The authors feel that immediate hysterectomy (with the avertin-antitoxin regime) was an important factor in the recovery of the patient.

R. J. WEISSMAN.

Sautter, Hans: Neuritis Nervi Optici During Lactation, *München. med. Wchnschr.* 87: 937, 1940.

Sautter discusses the comparatively rare disease of lactation neuritis of the optic nerve (amblyopia), citing two cases from the Tübingen Eye Clinic. He reviews the literature on the subject, giving the clinical picture, course, prognosis, and therapy. Lactation should be stopped immediately, general tonics prescribed besides administering ovarian hormone and B₁ vitamin preparations. The exact etiology of this condition is still an unsolved problem.

C. E. PROSHEK.

Sheehan, H. L.: Postpartum Necrosis of the Anterior Lobe of the Pituitary, *Lancet* 2: 321, 1940.

In four years the author has found in the autopsy material at the Glasgow Royal Maternity Hospital 25 cases with varying degrees of recent and healed necrosis of the anterior lobe of the pituitary gland. Ten cases are recorded in this paper. The lesion is due to collapse of the patient at delivery, usually associated with severe obstetric hemorrhage. If the patient survives and a significant necrosis is present, symptoms of hypopituitarism develop. The author believes that this is the etiology of most cases of true Simmond's disease.

CARL P. HUBER.

Tisne, L.: *B. Perfringens* Septico-toxemia, *Bol. Soc. chilena de Obst. y Ginec.* 6: 87, 1941.

Tisne cites two interesting cases of *B. perfringens* infection following induced abortion, the usual causal factor. The characteristic syndrome is produced by the toxemia more than by bacteriemia. Each case should be handled in two phases. The icterohemolytic manifestations, occurring early, may clear up, but the patient instead of recovering dies of hepatorenal damage. Principles of treatment successfully followed by Tisne are as follows: Cautious extraction of infected decidua, with irrigation of the uterine cavity with the new pure antiperfringens serum whose nonessential proteins have been removed by fermentation. A pack saturated with serum is left in the uterine cavity for twenty-four hours, then 160 c.c. of serum in saline are given daily in divided doses. Controlled by chloride determinations, 10 to 20 Gm. of salt (100 to 200 c.c. of 10 per cent by vein) are given daily and 20 Gm. sodium bicarbonate are given by mouth daily. Cardiovascular stimulants as needed. If the patient is not improving on this regime and uremia is progressing, decapsulation of one or both kidneys may be done. As soon as it is apparent that hemolysis has ceased, frequent 200 c.c. transfusions and fluids are in order. Vitamins are administered as indicated.

R. J. WEISSMAN.

Wu, C. J.: Hemolytic Streptococci From Parturient, *Chinese Med. J.* 60: 109, 1941.

Of 406 strains of hemolytic streptococci isolated from 1,055 parturient women, 114 belonged to Lancefield Group A, 2 to B, 156 to C, and 133 to G.

Of 345 women whose vaginal cultures were positive for hemolytic streptococci 68 had febrile puerperium, and of these febrile cases 51 were associated with Group A, 10 with Group C, and 7 with Group G organisms.

A considerable number of patients harbored the pathogenic Group A streptococci in their vagina without showing sepsis in the puerperium. This together with the fact that most febrile cases were mild, suggests that they were either dealing with Group A strains of low virulence or with a population possessing a high degree of immunity to streptococcal infections.

Simultaneous throat cultures done on these patients gave evidence that autogenous sources of infection did not play more than a trifle role in the causation of sepsis following childbirth.

C. O. MALAND.

Correspondence

Eight-Hour and Twenty-Four-Hour Pregnancy Test

To the Editor:

Under date of December 31, 1941, I received a letter from Prof. Bernhard Zondek from Jerusalem, Palestine, calling to my attention that he, previously, had attempted to shorten the pregnancy test by methods similar to the one we published recently (R. T. Frank and Rose L. Berman: A Twenty-Four-Hour Pregnancy Test, *AM. J. OBST. & GYNEC.* 42: 492, 1941). His efforts were nullified by the finding that in uterine fibroids, amenorrhea, menopause, castrates and carcinoma, the increased follicle-stimulating factor present produced *false positive reactions*. He does not mention either the quantity of urine injected or the species of animals used. (Bernhard Zondek: *Die Hormone des Ovariums u. des Hypophysenvorderlappens*, ed. 2, Vienna, 1935, p. 563).

Up to the present, in 385 reactions, 11 were on women with fibroids. Of these, 3 gave positive reactions (all later proved pregnancies) and 8 showed negative reactions (all proved nonpregnant by either curettage or hysterectomy). Of six menopause patients, 4 castrates, all gave negative responses as did 4 cases of amenorrhea of long standing. We have not had the opportunity of studying cancer patients.

Prof. Zondek likewise called my attention to two reports overlooked by us in the study of the literature. Reiprich, W.: Eine neue Schwangerschafts-schnell Reaction, *Harn. Klin. Wchnschr.* 12: 1441, 1933, who injected 10 to 14 c.c. of urine into 40 to 50 Gm. rats and read the reaction in thirty hours (increase in size by 2 x 3 times of the ovaries together with hyperemia). Walker (T. F.) and Walker (D. V. H.) (A Modification of the Aschheim-Zondek Test, *J. A. M. A.* 111, II: 1460, 1938) who injected one thirty- to forty-five-day-old rat with 1.5 c.c. of urine 3 times in one day, killing the animal after thirty hours (increase in size of ovaries, hyperemia, hemorrhagic follicles). Kelso (R. E.) (whom we had mentioned in our bibliography) likewise used the immature rat. In spite of the smaller quantity of urine injected, he obtained 3.8 per cent of false positive reactions in 130 tests.

Our further experience with the test has convinced us of its reliability, ready applicability, and inexpensiveness. In the eight-hour test, mentioned as an addendum, *positive* reactions may be relied upon, but *negative* reactions should be confirmed by performing the twenty-four-hour test additionally. Even in four hours, positive reactions have been obtained but further study will be necessary before the reliability of these shorter observations will be considered trustworthy.

R. T. FRANK.

New York, N. Y.

Feb. 26, 1942.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Thursday, June 4, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Group A, Part II, candidates will be scheduled for examination the first part of the examination period, and Group B, Part II, the latter half. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reevaluation* in Part II must make written application to the Secretary's Office before April 15, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Postgraduate Courses in Obstetrics at Chicago Lying-in Hospital

Five postgraduate courses in obstetrics, each of four weeks' duration, will be offered at the Chicago Lying-in Hospital between January 12 and June 6, 1942. These are sponsored by the Illinois State Department of Health and the Children's Bureau of the U. S. Department of Labor. The features of the program consist of observations on current managements of normal and abnormal states of the pregnant, parturient, and puerperal patient. Lectures, demonstrations, clinics, and other teaching means augment the operating room and birth room observations, and ward round discourses. The course is run on a non-profit basis. A deposit of \$25.00 is required on registration, \$10.00 of which is refunded at the completion of the course. All the members of the department participate in giving the courses. Additional information and application blanks may be obtained by request from Postgraduate Course, Department of Obstetrics and Gynecology, 5848 Drexel Avenue, Chicago, Illinois.

American Board of Obstetrics and Gynecology

In order to keep its records as up-to-date as possible during the present military emergency, the American Board of Obstetrics and Gynecology will appreciate receiving information about its Diplomates who hold either an active or a reserve commission in the Army or the Navy or the Public Health Services, or who are engaged in other official governmental duties or appointments. Diplomates, or their families, are requested to advise the office of the secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pennsylvania, regarding such appointments.

Erratum

In the article "Blood Transfusion in Pregnancy" by Dr. E. G. Hamilton and A. P. Martini, February issue, page 318, the thirteenth line from the bottom of the page should read: "It is doubtful if *slightly* hemolyzed blood, otherwise compatible, would produce such a severe reaction."

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society. *President*, W. C. Danforth, Evanston, Ill. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting, May, 1942, Sky Top, Pa.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, White Sulphur Springs, Va., September 9-11, 1942.
- Central Association of Obstetricians and Gynecologists. *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, Des Moines, Ia., October, 1942.
- South Atlantic Association of Obstetricians and Gynecologists. *President*, Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Next meeting, February, 1943, Pinehurst, N. C.
- A. M. A. Section on Obstetrics and Gynecology. *Chairman*, W. T. Dannreuther. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.
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- Brooklyn Gynecological Society. *President*, Bruce A. Harris. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society. *President*, Abraham Samuels. *Secretary-Treasurer*, Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society. *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society. *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology. *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
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- Pacific Coast Obstetrical and Gynecological Society. *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, San Francisco, Calif., November, 1942.

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- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, H. C. Walser. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
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- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.

Books Received

THE PREVENTION OF DEFORMITIES IN CHILDHOOD. By Richard Beverly Raney, Associate in Orthopaedic Surgery, Duke University, School of Medicine, etc. In collaboration with Alfred Rives Shands, Medical Director, DuPont Institute of the Nemours Foundation, Wilmington, Delaware, etc. Illustrated by Jack Wilson. Published and distributed by National Society for Crippled Children in the U. S. A., Inc., Elyria, Ohio, 1942.

ROENTGEN TREATMENT OF INFECTIONS. By James F. Kelly, Professor and Director of the Department of Radiology, Creighton University School of Medicine, etc., with collaboration of D. Arnold Dowell, Assistant Professor of Radiology, Creighton University School of Medicine, etc. 432 pages with 122 illustrations and charts. The Year Book Publishers, Inc., Chicago, 1942.

THE AUTONOMIC NERVOUS SYSTEM. By James C. White, Assistant Professor and Tutor in Surgery, Harvard Medical School, etc., and Reginald H. Smithwick, Instructor in Surgery, Harvard Medical School, etc. Second edition. 469 pages with 92 illustrations. The Macmillan Company, New York, 1942.

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American Journal of Obstetrics and Gynecology

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Original Communications

SEROUS ADENOFIBROMAS AND CYSTADENOFIBROMAS OF THE OVARY

ROGER B. SCOTT, M.D., BALTIMORE, MD.

*(From the Department of Gynecology, Johns Hopkins School of Medicine and
Johns Hopkins Hospital)*

IN RECENT years we have encountered in our laboratory and have had sent to us from other clinics several examples of ovarian tumors which we have designated as serous adenofibromas and cystadenofibromas. The paucity of the English literature dealing with this type of tumor is impressive. Although rare, they constitute a definite subgroup of serous epithelial tumors of the ovary. In a review of the case reports of ovarian tumors in our files for the last twenty years, embracing a total of 26,000 gynecologic cases, 13 case reports of such tumors were discovered and collected, and one report was found in the general pathology files. Not all of these specimens came from our operating room, for many were sent here from other hospitals, some in Baltimore and some in other cities. It is interesting to note the various diagnoses under which these tumors are filed, particularly the older cases: fibromas, fibromas with inclusion cysts, cystic fibromas, serous cystadenomas or papillary serous cystadenomas, solid adenomas, etc.

The only report in the English literature of a tumor of this type is the case report of Wolfe²² in 1927. The most complete report of the general subject is that of Oskar Frankl⁶ in 1927. In this he describes seventeen cases of "fibroma ovarii adenoeysticum." From the data

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

available in Frankl's article and in the light of more recent knowledge, it seems that many of his seventeen cases are incorrectly classified. As Dworzak² and Meyer have pointed out he included in the group a number of Brenner type neoplasms which showed various degrees of the pseudomucinous cystic change seen in some Brenner tumors. At least four cases must be eliminated from his group. Certainly the cases reported in a later article (1934) by Oskar Frankl and Klawns⁷ are examples of Brenner tumors. Neumann¹⁴ reports two cases, one an adenofibroma and one a papillary cystadenofibroma, while the one reported by Fleischmann⁵ in 1916 as "adenofibroma cysticum papillare ovarii" fits into this class except that the author describes solid cell nests. This again makes one suspect that the growth may also have been a Brenner tumor.

A review of the literature up to 1937 is found in the contribution by Robert Meyer in Henke and Lubarsch's *Handbuch der Speziellen Pathologischen Anatomie und Histologie*.¹³ Even here there is insufficient data available in many of the cases cited, and absolute inclusion in this specific group is a matter of conjecture.

For example a case included by Spencer¹⁸ in his report (1923) of ten ovariectomies in women over seventy years of age most certainly represents only cystic degeneration of an ovarian fibroma. Dworzak,² in 1932, reported a case which can unequivocally be considered a bilateral cystadenofibroma. Frankl's "fibroma ovarii adenocysticum" has been included as a special type of serous cystadenomas in Taylor's²⁰ recent suggested classification of ovarian tumors. This author suggested that the grossly solid Brenner variety with microscopic cysts having pseudomucinous lining be included as a special type under pseudomucinous cystadenomas. All in all, the literature on this type of ovarian neoplasm is extremely scant and much of it is questionable because of incomplete descriptions and more recent conceptions of various tumor types.

Wolfe described adenofibromas as "complex tumors of benign type in which epithelial and stromal elements simultaneously multiply." These tumors may grossly be quite minute (even microscopic) or very huge. The more solid type closely resembles the fibroma of the ovary or the solid Brenner tumor. The tumor is firm and compact, but minute cystic spaces may often be seen with the naked eye, while at times these cystic spaces may be relatively large. The intervening tissue is firm and white, with often a whorled arrangement of the strands of dense connective tissue. The cystic portions may enlarge, though rarely dilating in multilocular fashion, so as to occupy a large area of the tumor mass and to resemble the common serous cystadenomas. But, for inclusion in the group of cystadenofibromas at least a fourth of the total mass must remain solid, except perhaps for the presence of minute cysts. The more solid variety deserves the name of adenofibroma.

Interesting variations in size and position have been observed. The tumor in its early stage may appear as a tiny, dense, whitish area which stands out from the surrounding cortex, or it may produce only a minute raised area on the surface of a normal sized or slightly enlarged ovary. In other cases it may gravitate as an easily delineated nodule to a subcortical area and even to the hilus, or it may appear on the surface

as a small papilloma which on gross examination would be termed a papillomatous fibroma until stained sections revealed its adenomatous character. Even such small nodules may show marked dilatation of one or more of the cyst spaces, so that they are then more properly classed as small cystadenofibromas. In some instances the neoplasm may be multiple. In older literature one finds reports of much larger tumors than we encounter in our present, early-surgery period, and some of our own cases represent accidental findings at the operating table or in the pathology laboratory. The character of the fluid in the small and larger cyst spaces is usually thin and clear, serous in type, but in some cases it is thick and albuminous, and it may have a brownish tint.

Microscopically it is possible to establish a common denominator in the explanation of the various gradations of these tumors. As stated by Wolfe there are two constituent elements, the glandlike or cyst spaces and the fibromatous stroma. All of the small and large cyst spaces are lined by cuboidal or columnar, compactly placed, usually single-layered epithelium. The epithelium may be from two to four cells thick in areas, but this is uncommon and in many instances represents only tangentially cut portions. The nuclei are centrally or basally placed and are rather dark staining and elongated or circular. The cytoplasm is fairly uniform and moderately eosinophilic. Many and not uncommonly the majority of the epithelial cells have cilia. The adenomatous areas may be circular, elongated, or quite irregular. One often sees a papillary projection from the lining wall into the cyst spaces; these outgrowths have a dense fibrous core and are covered by the same type of epithelium as that lining the cysts. A papillary tendency was not usually seen on the surface of the tumor except in the case of the small cortical type, in which case the papillae were covered with germinal epithelium which frequently showed stratification. The so-called "psammoma-bodies" so often found in the serous cystadenomas are not uncommon in the adenofibromas and cystadenofibromas, particularly those of small size. They seem to develop as a result of calcification in the typical small glandlike space, and in one of our cases various transition stages, from early partial calcification of a cyst space and its lining epithelium to complete replacement, could be demonstrated. The stroma is exactly similar to the stroma of the common fibromas. There are compact bands and narrow strands of fibrous tissue running in all directions, often whorled, and much collagen can be found between the separate fibers. The connective tissue reaction is much more marked immediately about the cyst spaces, and in a few of the smaller tumors this pericystic reaction was the only evidence of fibromatous proliferation. With Van Gieson's stain all of this stromal tissue appeared to be connective tissue, but with the Masson's trichrome stain the fibers immediately about the cyst spaces took a peculiar red stain, like that of very young smooth muscle tissue.

Carcinomatous or sarcomatous changes would seem to be as possible in these tumors as in the serous cystadenomas or fibromas. The malignant change, when fully developed, so distorts the picture that it would be difficult to determine the nature of the benign precursor in many cases. None of our own tumors were malignant microscopically, and none of the patients later developed malignant changes in the contralateral ovary when it was conserved, in as far as we have been able to determine from the follow-up of the patients.

The gross picture and its variations, as well as the characteristic microscopic picture, will seem clearer when the case reports are studied and when the question of etiology is discussed. A short summary of the clinical and pathologic data in these fourteen cases is presented below. Unimportant and unnecessary detail has been eliminated as much as possible and in all cases when the typical lining epithelium is referred to this will mean the cuboidal or columnar, often ciliated type.

CASE 1.—(Gyn. Path. No. 29902.) This is a 52-year-old white female who complained of a crampy, aching abdominal pain for the previous six months. This pain was most marked in the left lower quadrant. Other facts in the history were of no importance and the menstrual history was normal. She was never married and never pregnant. The menopause was two and one-half years ago and she had had occasional hot flushes. On examination a tumor mass was found in the right adnexal region, and on Dec. 3, 1924, at Church Home Infirmary, Baltimore, Dr. T. S. Cullen removed the right ovarian tumor, the right tube, and the appendix. The other pelvic organs were noted as normal at operation. The specimen was sent to the Johns Hopkins Hospital laboratory and the ovarian tumor was found to be a bilobed, firm mass; the slightly larger lobe of which measured 4 by $2\frac{1}{2}$ by 2 cm. On section both lobes were seen to be made up of firm, white, fibrous tissue in which there were numerous small, smooth-lined, glistening cavities. Microscopically the tumor showed dense fibrous tissue in whorls, most dense about the small cystic spaces lined by the typical epithelium. The largest cyst space measured 4 mm. in diameter.

Diagnosis.—Serous adenofibroma, ovary, right. Salpingitis, chronic, right. Normal appendix.

Nothing has been heard of the patient since the time of operation.

CASE 2.—(Gyn. Path. No. 38202.) This was an 87-year-old white female who complained of vague abdominal discomfort for the past one and one-half years. She was married but had never been pregnant, and the menopause was uneventful forty years previously. There was never any abnormal vaginal bleeding. Upon examination by her family physician, an abdominal tumor was found extending to the umbilicus. On April 28, 1932, at St. Agnes Hospital, Baltimore, Dr. Emil Noyak did a total abdominal hysterectomy and a bilateral salpingo-oophorectomy. The specimen was sent to the Johns Hopkins Hospital pathology laboratory. The right ovary was replaced by a huge cystic tumor, 18 cm. in diameter, whose wall was thin except for about one-third of the total mass which was solid and quite firm. The cyst was filled with clear, straw-colored fluid, although there were some smaller locules filled with

old blood. Many of the locules presented minute papillary projections on the inner surface. The left ovary showed two small cysts filled with clear, straw-colored fluid. On microscopic section, these were found to be typical small serous cysts. The right ovarian tumor showed the same type of cyst wall with cuboidal to low columnar, often ciliated, epithelium, and at areas there were papillary projections into the cysts. The solid portion was densely fibrous with numerous small cysts lined with the same type of epithelium; a few of these smaller cysts also had papillary growths from the wall.

Diagnosis.—Papillary serous cystadenofibroma, ovary, right. Serous cysts, ovary, left. Atrophic cervix with Nabothian cysts. Endometrial polyp. Atrophic endometrium, myometrium, and tubes.

The patient has not been seen since operation and no information can be secured as to her status.

CASE 3.—(Gyn. Path. No. 38437.) This was a 60-year-old white female who was first seen with difficulty in breathing and with vomiting for several hours prior to admission to the hospital. There had been considerable epigastric pain and on examination the abdomen was diffusely tender. A mass of an uncertain character was felt in the pelvis. No data were obtained of the previous health or the menstrual history. On June 17, 1932, at St. Agnes Hospital, Baltimore, Dr. Oliver did a bilateral oophorectomy, myomectomy (three small subserous nodules), and a cholecystectomy. A large calculus was found in the gall bladder. The ovarian tumors were sent to the Johns Hopkins Hospital Gynecologic Pathology laboratory, and they were both found to be about 6 cm. in diameter and fairly globular in outline. One tumor was solid and of a firm, fibrous nature on section. The other tumor was thick walled (about 1½ cm.), and in this wall minute cystic spaces were seen. There was a large cyst, occupying the central portion of the tumor and this was filled with clear, mucinous material. There were a few papillary projections on the wall of the cyst. On microscopic examination the solid tumor was found to be a typical fibroma, and the opposite one had a cyst lining of the typical epithelium; distributed throughout the firm fibrous wall were numerous small glandlike spaces lined by the same epithelium.

Diagnosis.—Papillary serous cystadenofibroma, ovary, one side. Fibroma, ovary, other side. Myomata uteri, subserous. Cholelithiasis and chronic cholecystitis. This patient cannot be traced.

CASE 4.—(Gyn. Path. No. 44921.) This was a white woman, 60 years of age, who complained of vaginal bleeding of two years' duration, more intense in the past three weeks. The menses were regular and the menopause occurred eight years previously. There had been four pregnancies, and one of these resulted in an early miscarriage. The youngest child was thirty years of age. On examination bilateral adnexal masses were felt. On Dec. 2, 1936, Dr. Harry M. Nelson at the Womens Hospital, Detroit, Michigan, did a hysterectomy and a bilateral salpingo-oophorectomy. Dr. D. C. Beaver, director of the laboratory at this Hospital, sent Dr. Novak slides and photographs of these tumors. The photographs are self-explanatory for gross description (Figs. 1 and 2); the left, solid tumor measured 4.5 by 4 by 3 cm. and the right, partially cystic one, measured 5 by 4 by 4.5 cm. Microscopically there was the fibrous tissue overgrowth with many small cystic spaces lined by the

typical epithelium. The large cyst had the same type of lining epithelium, and on both sides papillary projections from the wall of the cyst spaces were seen. Psammoma bodies were seen on both sides.

Diagnosis.—Papillary serous adenofibroma, ovary, left. Papillary serous cystadenofibroma, ovary, right. Atrophic endometrium and endometrial polyps (which probably accounted for the postmenopausal bleeding).

This patient at present is alive and well, according to correspondence from Drs. Beaver and Nelson.



Fig. 1.—Case 4. Gross picture of the serous adenofibroma which replaced the left ovary. Psammoma bodies and minute papillary projections into many of the tiny cyst spaces were seen microscopically. About actual size. See Fig. 2 for tumor of the opposite ovary.



Fig. 2.—Case 4. Gross picture of the serous cystadenofibroma which replaced the right ovary. Psammoma bodies and a papillary tendency were seen on this side as in Fig. 1. A small accumulation of papillary projections can be seen here at the upper border of the largest cyst. About actual size.

CASE 5.—(Gyn. Path. No. 45368.) A 42-year-old colored female complained of pain in both lower quadrants for five weeks, prolonged menses, and continuous vaginal bleeding for the previous month. She had been admitted to the Hospital three months prior with a diagnosis of sub-acute salpingitis and pelvic peritonitis. Sulfanilamide therapy was given at this time with apparent good results. She had had two previ-

ous pregnancies and full-term deliveries; the youngest child was twenty-three years old. Bilateral tender adnexal masses were felt, and on July 28, 1937, Dr. Laman Gray did a subtotal abdominal hysterectomy and bilateral salpingo-oophorectomy. The right ovary showed a papillomatous, firm projection from the surface, about 1 cm. in greatest diameter. On microscopic section this was found to consist of dense fibrous tissue with a few very small, glandlike spaces lined by columnar or cuboidal epithelium.

Diagnosis.—Surface serous papillomatous adenofibroma, ovary, right. Endometrium, interval, non-secretory. Myomata uteri, intramural and subserous. Pyosalpinx, bilateral. Abscess, ovary, bilateral.

She was seen two and one-half years later, and although she had numerous complaints, examination, including pelvic, was without significant findings.

CASE 6.—(Gyn. Path. No. 46139.) A 58-year-old colored female was admitted with the complaint of left lower quadrant pain at intervals over the previous three years. Menses were always regular, and the menopause was uneventful eight years previously. She had three pregnancies: one a miscarriage, one a stillborn, and one a full-term delivery in which the infant died at the age of six months. Nodular pelvic masses were felt, and on Jan. 26, 1938, Dr. T. S. Cullen did a bilateral salpingo-oophorectomy. The right cyst was 10 cm. in diameter and the left was 3.5 cm. in greatest diameter. The cysts were multilocular and filled with clear, straw-colored fluid. In each there were dense solid portions which made up about one-half of the tumor mass. The fibromatous reaction and the small gland spaces with the typical lining epithelium were again seen in the solid portions on stained sections. The larger cysts were also lined with this epithelium.

Diagnosis.—Serous cystadenofibromas, ovary, bilateral. Atrophic tube, bilateral.

This patient was well except for occasional hot flushes two and one-half years after operation.

CASE 7.—(Gyn. Path. No. 48600.) This was a 31-year-old colored female who complained of pain in both lower quadrants of the abdomen for the previous nine months, and this pain had become constant in the left lower quadrant for the past three weeks. Over the previous year she had noted increasing enlargement of the abdomen. Menses were always regular and she had had two pregnancies, both of which ended in miscarriages one and two years previously. On examination a large cystic mass was found arising from the right adnexal area and extending to just above the umbilicus. On May 31, 1939, Dr. Henry Bennett did a right salpingo-oophorectomy. The cyst was found to be twisted slightly and adherent. On examination the mass was found to consist of two large cysts, and measuring 15 by 16 by 11 cm. and 16 by 20 by 9 cm., respectively. These were filled with thick, dark brown, gelatinous material, and there were several daughter cysts in the wall. Several small papillary projections were seen protruding into one of the cysts. The wall was 1 to 4 mm. thick, except at one border where there was a dense, firm, solid mass 5.5 cm. in its greatest diameter. The ovary was distinctly outlined and separate, except that the solid mass described was attached to one pole. The ovary measured 3 by 5 by 1.5 cm., and it contained a few small follicle cysts on section. The

solid part of the neoplastic mass revealed the characteristic fibrous stroma with small cystic spaces lined by the typical epithelium. The cyst walls all had the same type of lining and there were numerous small and moderate-sized papillary projections from the wall into the cysts. Psammoma bodies were frequent.

Diagnosis.—Papillary serous cystadenofibroma (papillomatous in type), ovary, right. Perisalpingitis, chronic, right. This patient was seen again two years after discharge and pelvic examination revealed the uterus to be adherent to the left, and there were no palpable adnexal masses.

CASE 8.—(Gyn. Path. No. 50470.) This was a 69-year-old white female who ceased menstruating at fifty-two years of age for a period of six months and then began to have apparently normal menses every three to six months. In September, 1939, she began to bleed continuously and a curettage at that time revealed adenocarcinoma of the fundus uteri. A full course of radium therapy was given. She had had six pregnancies and full-term deliveries; the youngest child was thirty-five years old. The menses were not unusual before the onset of the present illness. On examination at Johns Hopkins Hospital the uterus was found to be about three times normal size, and a partially cystic mass, about 7 cm. in diameter, was felt in the right adnexal area. On May 14, 1940, Dr. Richard TeLinde did a total abdominal hysterectomy and a bilateral salpingo-oophorectomy. The right ovarian tumor measured 8 by 4 by 3 cm. and one-half of this tumor was solid, the other half being cystic. The cystic part was filled with thin, clear fluid, and there were a few papillary processes in the cyst wall. Microscopically the section showed the fibromatous overgrowth with the small cystic spaces and the usual epithelial lining of both the small spaces and the larger cysts. Papillary projections were prominent and a few of the fibrous areas showed a moderate amount of hyaline degeneration.

Diagnosis.—Papillary serous cystadenofibroma, ovary, right. Cervicitis, chronic. Adenocarcinoma, fundus, uteri. Myomata uteri, subserous. Atrophic tube, bilateral. Atrophic ovary, left.

All efforts to contact this patient since discharge have failed.

CASE 9.—(Gyn. Path. No. 51214.) This was a 55-year-old white female whose chief complaint was pressure in the rectum. She had had a uterine suspension, appendectomy, and right oophorectomy ten years previously. Menses were normal, and the menopause occurred eight years prior to admission. This patient was operated upon in Binghamton, New York, by Dr. Francis O'Neill, and a description of the gross tumor and sections were sent to Dr. Novak at this Laboratory by Dr. Victor W. Bergstrom, Director of the Kilmer Pathological Laboratory, Binghamton, on Sept. 1, 1940. The tumor measured 11 by 8 by 4 cm., and it was somewhat nodular. On section there was a thin fibrous capsule and the tissue was yellowish, dense, fibrous, and often arranged in whorls. Stained sections showed the small glandlike areas in a dense fibrous field. The epithelial lining of these spaces was of the typical type.

Diagnosis.—Serous adenofibroma, ovary, left.

The patient is now living and well.

CASE 10.—(Gyn. Path. No. 51446.) This was a 46-year-old white female who complained of vaginal bleeding of thirty-three days' duration. Menses were always regular, and there were no data given as to her previous pregnancies, if any. On examination the uterus was retroflexed and very nodular. On Oct. 24, 1940, at Bon Secours Hospital,

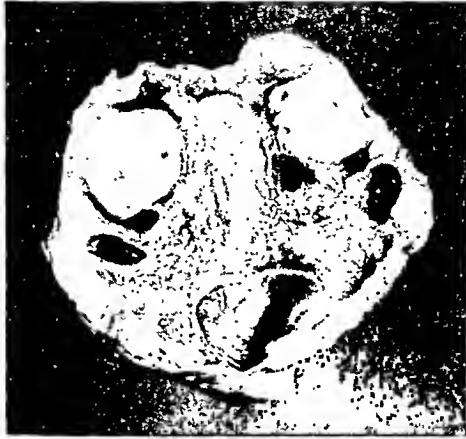


Fig. 3.—Case 10. Cross section of the left ovary, approximately actual size. The two cortical adenofibromas, extending subcortically, are easily seen, and the cyst at the bottom was found to be a typical small serous cyst.

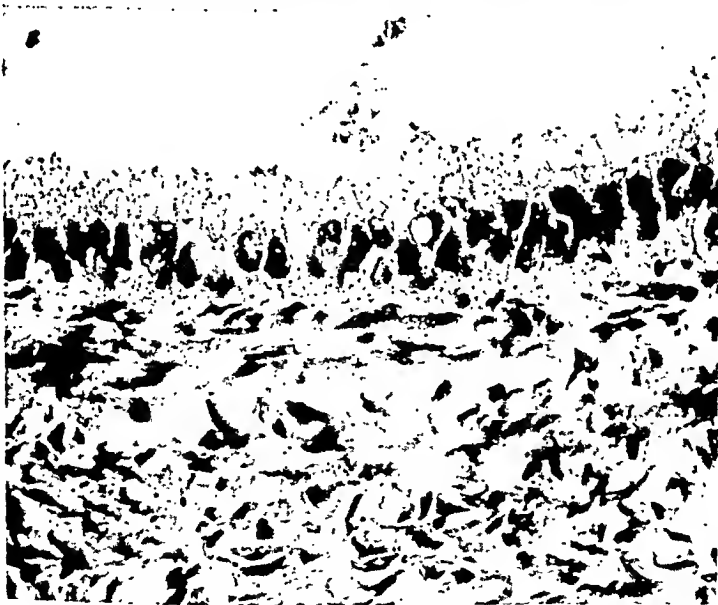


Fig. 4.—Case 10. High power ($\times 550$) of the typical, single-layered, columnar epithelium lining the "glandlike" spaces. Ciliated cells were more abundant here than in most of these neoplasms.

Baltimore, Dr. Emil Novak did a subtotal, abdominal hysterectomy and a right salpingo-oophorectomy. The right ovary was slightly larger than normal and the surface was smooth. On section two subcortical, solid nodules, were seen, the largest measuring 1.2 cm. in diameter. At the operating table these were thought grossly to be

small Brenner tumors. Microscopically the solid areas contained small cystic spaces and one large cystic space (0.7 mm. in diameter), all of which were lined by this typical epithelium. The spaces were imbedded in a dense fibrous stroma.

Diagnosis.—Serous adenofibromas, ovary, right. Serous cyst, ovary, right. Endometrial hyperplasia. Myomata uteri, intramural. Normal tube, right.

This patient is alive and well one and one-half years postoperatively.

CASE 11.—(Gyn. Path. No. 51534.) This was a 40-year-old colored female who complained of pains off and on for twelve years in the left lower quadrant of the abdomen and of an abdominal tumor which she had felt for the past year. In this previous year she had backache and rather marked frequency of urination without burning. Menses were always regular, and there had been one pregnancy and full-term delivery nineteen years previously. On examination the uterus was replaced by a nodular mass extending to about midway between the symphysis and the umbilicus and filling the adnexal areas. On Nov. 22, 1940, Dr. Henry Bennett did a subtotal abdominal hysterectomy, salpingo-oophorectomy, right, salpingectomy, left, resection of small ovarian cyst, left, and appendectomy. The right ovary measured 3.5 by 2.5 by 1 cm. and the surface was wrinkled. On section a few small cysts were seen filled with clear, thin, fluid. Microscopically there was a central area 8 by 4 mm. which contained numerous small cysts of irregular shapes and without much fibrous reaction about them. In a microscopic area (1.5 mm.) just to the side of the cystic portion there was a denser portion in which were imbedded many small glandlike spaces. The fibrous tissue proliferation was more extensive here. The epithelial linings of all of these spaces and of the more cystic area described were of the typical type.

Diagnosis.—Serous adenofibroma, ovary, right. Endometritis, chronic. Myomata uteri, intramural and subserous. Salpingitis, chronic, left. Salpingitis, isthmica nodosa, right. Endometrial cyst, ovary, left. Normal appendix. Postoperatively the patient developed an incisional infection and later a ventral hernia. On June 11, 1941, this hernia was repaired and pelvic examination revealed no enlargement of the remaining left ovary. She is now asymptomatic.

CASE 12.—(Gyn. Path. No. 52448.) This was a 29-year-old white female who complained of pain in the right lower abdomen for the past year. Menses were always regular. She had had three early spontaneous abortions in the previous five years, the last one being in April, 1940. Appendectomy was done at the age of thirteen. A small mass was felt in the region of the right ovary, and on April 30, 1941, Dr. Richard TeLinde did a right salpingo-oophorectomy. The right ovary was densely adherent to the adjacent structures. It measured 5 by 4 by 2 cm. The surface was covered with many fibrous tags, and there were about ten slightly elevated, small, firm areas. On section these firm areas were found to be minute cortical, dense, white structures. Microscopically these cortical areas showed heavy fibrous proliferation and numerous small cysts, all lined by the same type of epithelium seen lining germinal inclusion cysts. The areas were quite distinctly outlined and separate from each other. Many psammoma bodies were seen in all stages of formation.

Diagnosis.—Small serous adenofibromas, ovary, right. Follicle cysts and corpus luteum, ovary, right. Salpingitis, isthmica nodosa, right.

The patient is now well except for some persisting slight pain in the left lower quadrant.

CASE 13.—(Gyn. Path. No. 52750.) This was a 58-year-old white female who complained of brownish vaginal discharge which at times contained blood for the previous thirteen years. Thirteen years ago she had an ovarian cyst removed at another hospital, and no data were available, except that the patient said that it weighed thirty-one pounds. She never menstruated following this operation. Prior to the operation she had had two full-term, rather difficult, deliveries. A curettage was done by Dr. Leo Brady and the curettings showed adenocarcinoma of



Fig. 5.—Case 12. Low power ($\times 50$) of a portion of one of the cortical adenofibromas in this case, showing the small "glandlike" spaces, the fibromatous proliferation, many psammoma bodies, and the surface papillary tendency.

the fundus uteri. Following 3,600 mg. hours of intrauterine radium and 6,000 r. units of deep x-ray therapy, Dr. Brady on June 16, 1941, did a total abdominal hysterectomy, right salpingo-oophorectomy, and appendectomy. The right ovary measured 3 by 2 by 1 cm., and projecting from one pole was a firm, white nodule which measured 1 cm. in diameter. On stained section the tissue of this nodule was dense and fibrous and scattered about were several small, irregular cysts which were lined by the usual epithelium.

Diagnosis.—Papillomatous serous adenofibroma, ovary, right. Atrophic cervix. Endometrium, postmenopausal, atrophic (no adenocarcinoma was found in numerous sections). Hypertrophy of uterus. Periuterine adhesions. Atrophic tube, right. Mucocoele of appendix.

The patient was clinically well one month after discharge.

CASE 14.—(Gyn. Path. No. 17071.) This 50-year-old white female came to autopsy ten hours following removal of a chromophobe adenoma

of the pituitary which had produced progressive loss of vision over three years. She was quite obese, never pregnant, and menses were always regular. The menopause occurred five years prior to admission. At the age of twenty, there had been a pelvic operation of an unknown character. At autopsy the left tube and ovary were missing, and there were several moderate-sized intramural myomas. The ovary was about normal size, and projecting from one side was a thin-walled cyst about 4 cm. in diameter. The cyst contained clear serous fluid and the walls were smooth. On section numerous minute cysts were seen in the ovarian substance below this attached large cyst. Microscopically there was in this ovarian area and extending centrally a large collection of minute cysts imbedded in a dense fibrous stroma. These cysts were lined with



Fig. 6.—Surface germinal epithelium ($\times 1200$) of the ovary of a 46-year-old white female. This demonstrates the cilia which may rarely be found on uninvaginated surface epithelium. (Gyn. Path. No. 53139.)

the typical epithelium, as was the large cyst which seemed to arise from this area. The solid area with many cysts was about 1.5 cm. in diameter. At the border of this intraovarian lesion there was a minute circular fibroma without cystic contents. Psammoma bodies were seen.

Diagnosis.—Serous cystadenofibroma, ovary, right. Normal tube, right. Myomata uteri, intramural.

In summary, therefore, our series includes 8 adenofibromas and 8 cystadenofibromas. One adenofibroma was associated with a cystadenofibroma of the opposite side, and in one case there were bilateral cystadenofibromas. Two adenofibromas and one cystadenofibroma were of the surface papillomatous type, and in 2 cases there were multiple cortical or subcortical adenofibromas. The remaining tumors completely or almost completely replaced the ovary. Only one adenofibroma presented papillary projections into the small cyst spaces, while 5 of the cystadenofibromas grossly or microscopically revealed this variation.

All but 4 of these tumors were palpable preoperatively, either as tumor masses or as enlarged, atypical ovaries; 3 of them [a surface papillomatous adenofibroma (Case 5), adenofibromas (Case 10), and an adenofibroma (Case 11)] were incidental laboratory or operating room findings, and the fourth was found at autopsy. Had a pelvic examination been done in this autopsy case the associated cyst could undoubtedly have been palpated.

The co-existing uterine, tubal, and contralateral ovarian pathology was without any apparent significance. The opposite ovary in 2 cases presented the same type of tumor or a variant thereof, and in one case there was a large fibroma on the opposite side. In the other cases the opposite ovary was not removed at operation because of its normal character, or when removed it was normal or it revealed totally unrelated pathology (except for a serous cyst on the opposite side in one case and two serous cysts in the same ovary in another case). Myomas of the uterus were found in 6 cases. This may seem a high percentage, but in proportion to the incidence of myomas in our total operative cases, which include a large number of colored patients, it is not excessive. In many of these 14 cases the myoma was the sole or major contributing factor to operative intervention. Two of the 4 colored females in this series had myomas. Salpingitis and other pelvic inflammatory lesions were no more frequent than would be expected in any consecutive series in our Laboratory. The presence of adenocarcinoma of the corpus uteri in 2 cases is interesting, but of no great significance, except that it constituted the indication for operation in these patients.

In evaluating the symptoms, abdominal pain was the presenting complaint in nine of the cases. In one of the cases it was the pain of pelvic inflammatory disease and in another the pain of cholelithiasis. In one case pain was due to the pressure of large myomas. In the remaining 6 cases the pain was directly related to the ovarian neoplasm or neoplasms. In only 2 cases had the patient noted the tumor growth prior to operation.

Five patients complained of abnormal uterine bleeding. Superficially this might suggest that such tumors may exhibit endocrine properties, but in all of these cases the other existing pathology more adequately explained the bleeding:

- Case 4: Endometrial polyps
- Case 5: Myomata uteri, intramural and subserous; pyosalpinx, bilateral; abscess, ovary, bilateral
- Case 8: Adenocarcinoma, fundus uteri
- Case 10: Endometrial hyperplasia; myomata uteri, intramural and subserous
- Case 13: Adenocarcinoma, fundus uteri

In 11 of Frankl's cases there were urinary complaints, but in only one of my series was this noted, and in this case it was probably due to

pressure from myomas. This discrepancey in figures is probably explained by the great size of the tumors in Frankl's group.

Here, as in all other reported cases, the age incidence is found to be very characteristic.

TABLE I. AGE AND DISTRIBUTION OF CASES

AGE	FRANKL'S TYPICAL CASES	WOLFE	NEUMANN	DWORZAK	PRESENT	TOTAL
20-29					1	1
30-39					1	1
40-49	4	1	1		3	9
50-59	6				5	11
60-69	2		1	1	3	7
70-79	1					1
80-89					1	1
Totals	13	1	2	1	14	31

Other reported cases in which the pathologic diagnosis seems doubtful are not included in Table I. In these 31 cases, all but 2 are forty years of age or over (93.5 per cent) and all but 11 are fifty years of age or over (64.5 per cent). It is well known that with increasing age and ovarian atrophy, fibromatous reaction and replacement becomes more common, and with the corrugation of the surface and the invagination of the germinal epithelium, germinal inclusion cysts are a frequent finding. It is not surprising, therefore, that these tumors, the chief pathologic feature of which consists of fibrous tissue proliferation about numerous small "inclusion-like" cysts, should be more common beyond the fourth decade of life and particularly after the menopause.

Two patients of this group were one to five years postmenopausal, 3 were five to ten years, 2 were ten to twenty years, and 1 forty years. There were no accurate menstrual data on one patient, aged 60 years, who was obviously past the menopause. Dworzak felt that the early menarche and early menopause in his patient and in many of Frankl's patients were significant. Early menopause means early ovarian inactivity, and only in this way would it seem to play a part. A survey of these cases as to menarche, parity, and age of menopause shows no significant relationship.

The follow-up in many of these cases is not as adequate as one would desire. In those cases which we have been able to follow, there is no evidence that a similar tumor has developed in the remaining ovary, nor is there any evidence that these tumors were in any sense malignant. Microscopically there was no suggestion of malignancy, and the only alteration in the usual epithelial character was a slight piling up of the lining cells in some cases. Any one familiar with the microscopic picture of benign serous cystadenomas realizes that this is a frequent finding. As previously stated, it is conceivable that carcinoma might develop from the epithelial elements or sarcoma from the connective tissue.

We have not had an opportunity to trace such a transition, and were malignancy to occur, the gross and microscopic picture would probably be so altered that it would be impossible to say that the tumor might have originally been an adenofibroma or cystadenofibroma.

ETIOLOGY

Since the work of Robert Meyer¹² in 1916, practically all gynecologists are agreed that serous cysts and serous cystadenomas are derived from the germinal epithelium. Meyer felt that all ciliated epithelial tumors were derived from the germinal epithelium. Goodall,¹⁰ in 1920, demonstrated that the Wolffian tubules unite outside the ovarian structure in embryonic life and that the medullary rays and rete ovarii are derived directly from the germinal epithelium. Therefore, if serous tumors are derived from remnants of these structures in the adult ovary, they are indirectly of germinal epithelial origin. As Goodall states, there is no tissue in the human body which can equal the metaplastic power of this epithelium. Ciliated epithelial cells have been found on the surface of the ovary by Pfannenstiel,¹⁶ Flaischlein,³ Walthard,²¹ de Sinéty et Malassez,¹⁷ Goodall,¹⁰ and others. In several cases with corrugations of the surface and invaginations of the surface epithelium, the author has found ciliated epithelium, both in the sulci and over the gyri, although never as marked as in the germinal inclusion cysts.

The similarity of the epithelial lining of the cyst areas in the adenofibromas and cystadenofibromas to that of the invaginating surface epithelium and the germinal inclusion cysts places this group in the serous epithelial class. This agrees with the etiologic impression held by Dworzak and Wolfe. Wolfe feels that the beginning is a fibromatous surface sprouting from the ovarian cortex which is later invaded by the somewhat piled-up germinal epithelium. This burrows in narrow, zig-zag, elongated channels into the depths of the fibromatous stroma. The fact that the cyst spaces in the adenofibromas are comparatively regular in outline and the finding of small cortical and slightly larger central tumors would lead one to expect that the invagination preceded the fibromatous reaction and that the tumor then progressed centrally or peripherally. The cyst spaces probably multiply by budding and progressive invagination. We have called the surface fibromas, which show the long, twisting narrow epithelial channels in a dense connective tissue matrix, intracanalicular fibroadenomas, because of their striking resemblance to the well-known intracanalicular fibroadenomas of the breast. In the past twenty years in our laboratory, we have had 9 of these tumors, all less than 3 cm. in diameter and none as large as cited by Taylor.¹⁹ In our cases, we have not included those which were an integral part of an associated cyst and projected into it from the cyst wall. These were preponderantly in elderly females, and psammoma bodies were even more frequent than in the adenofibromas and cyst-

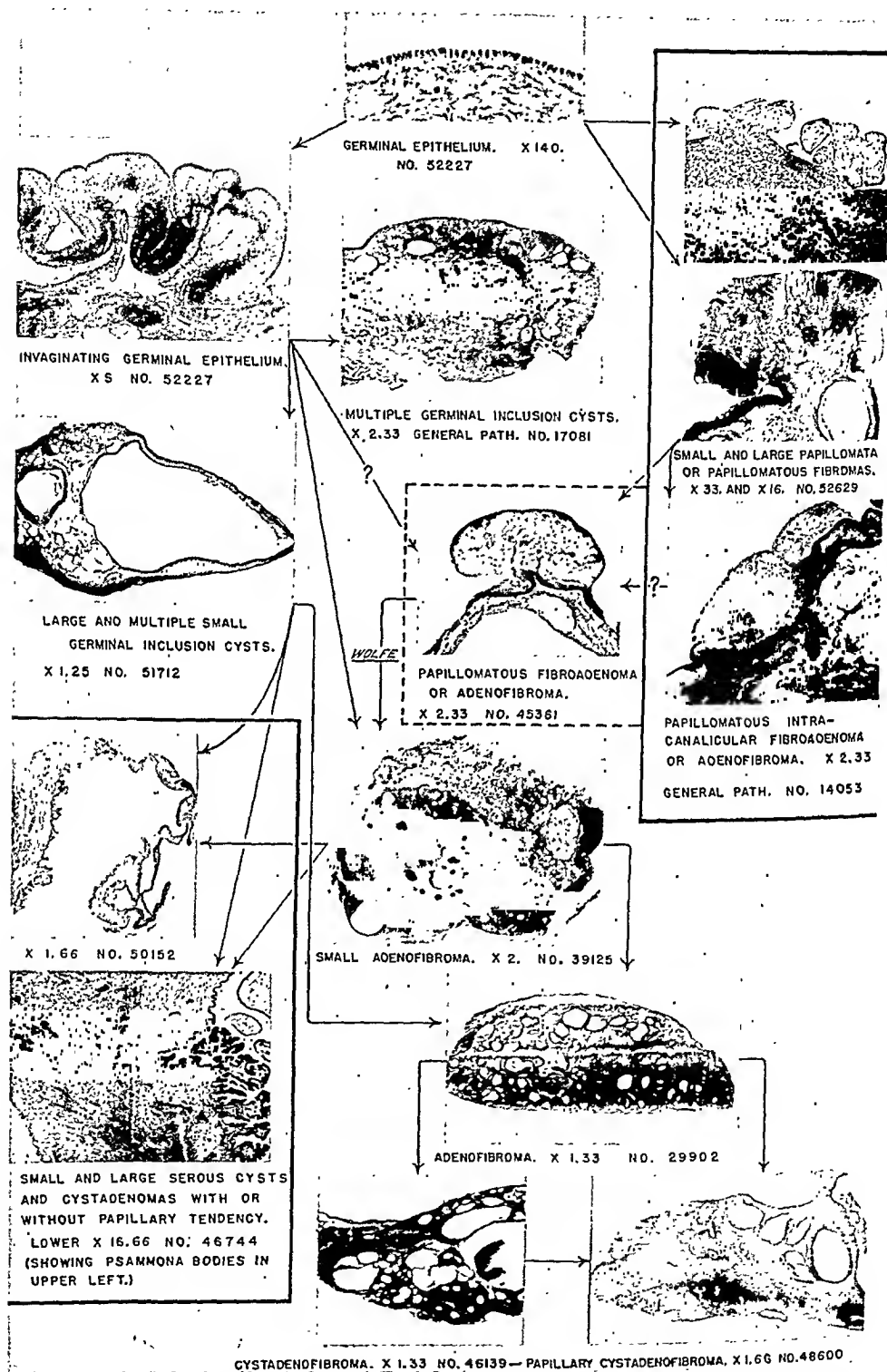


Fig. 7.—Photomicrographic diagram of the probable development of serous adeno-fibromas and cystadenofibromas from the germinal epithelium and the relationship to serous cysts and cystadenomas and papillomatous fibromas. For discussion see body of the paper under etiology.

adenofibromas. Microscopically one feels that these epithelial channels in the intracanalicular fibroadenomas are still connected with the surface.

Fig. 7 represents what most logically is the etiology of the adenofibromas and cystadenofibromas of the ovary. Our files have been searched for a typical example of each step in this process, and an effort has been made with these photomicrographs to be as graphic and understandable as possible. The tissues from which these tumors are derived are the germinal epithelium with its cuboidal and occasional peg-shaped, and often small round basal ("germinal"?) cells, and the underlying tunica albuginea, and fibrous cortical stroma. Some unknown factor can stimulate activity in these tissues in either of two possible directions. The fibrous stroma may begin to grow and produce the common papillomatous fibroma. The stromal proliferation in turn activates the overlying epithelium, and it is often seen to pile up, and it may penetrate the fibroma in narrow tortuous channels and form the intracanalicular fibroadenoma. On the other hand the epithelial channels, as Wolfe believes, may partially or completely be nipped off to produce a papillomatous adenofibroma or fibroadenoma. It is then possible for this to grow and become the large adenofibroma or cystadenofibroma. If this last step were the usual process, the ovary on this side would be expected to remain relatively distinct and attached at one pole, but this was not so in most of the large tumors of this series. More frequently the germinal epithelium invaginates from the ovarian surface, is pinched off, and produces germinal inclusion cysts. Gardner⁸ states that these are seen most commonly in the presence of pelvic inflammation and subsequent adhesions, but atrophic and atrophying ovaries of the female past forty years of age have been the site of predilection in our experience, as stated by Novak.¹⁵ As the epithelium dips into the surface sulci, it can often be seen to pile up slightly and to assume a more compact cuboidal or columnar character, and it is often ciliated; at times this epithelium resembles tubal and more rarely endometrial epithelium. The inward sprout of germinal epithelium is then compressed in its proximal portion, leaving a typical inclusion cyst. By budding of this sprout and by a similar process elsewhere, multiple cortical inclusion cysts are formed, or in other cases a distinct cortical or subcortical nodule of many small cysts and marked pericystic fibrous tissue proliferation. The isolated or widely distributed germinal inclusion cysts usually show little or no fibrous overgrowth about them. The single, large inclusion cyst or the definite nodule may enlarge primarily into a single or multiple cystic structure, constituting the well-known serous cyst or serous cystadenoma, with or without papillary tendency. The small adenofibroma may show neoplastic growth and may completely replace the ovary to form the large adenofibroma or, because of enlargement of some of the cyst cavities it gives rise to the cystadenofibroma, with or without papillary tendencies.

CLASSIFICATION

It seems that these tumors etiologically must be considered a special group under the serous epithelial tumors or, as Taylor has classified them, a special type of epithelial tumor under the heading of serous cystadenoma. It is not my wish further to complicate the already complicated classification of ovarian tumors, but these tumors comprise a definite group. The name of serous cystadenoma alone does not adequately describe tumors which include a solid, fibrous portion with the numerous, minute, "glandlike" spaces characterizing the cystadenofibromas. Certainly it is not adequate for the grossly solid or minutely cystic adenofibroma. If one-fourth or more of the total space occupied by the cystadenoma type of tumor is solid (in a fibroma-like manner), then it should be called a cystadenofibroma. The prefix of serous to these tumors is indicative of their etiology. Because of the possibility of malignant change, the epithelial elements must receive first consideration, and to classify the neoplasm as a mere variant of the fibromas would be unwise.

SUMMARY

1. Fourteen cases of serous adenofibromas and cystadenofibromas of the ovary are reported. These tumors correspond to the typical "fibroma ovarii adenoeysticum" of Frankl, and Wolfe's case in 1927 is the only one previously reported in the English literature.

2. The tumors were found to be made up of two component parts, a dense connective tissue matrix in which were imbedded numerous small cystic spaces lined by compact, single-layered, cuboidal or low columnar, often ciliated epithelium. "Psammoma-bodies" and papillary tendencies were frequent.

3. Grossly the tumors were firm and solid, with minute cystic spaces (adenofibromas) or partially cystic with at least one-fourth of the mass solid (cystadenofibromas).

4. In two cases the neoplasm was bilateral, and in 3 cases the neoplasm was an incidental laboratory finding.

5. There was no constant associated pelvic pathology of significance, although myomata uteri were found in 6 cases.

6. Pain was the most common presenting complaint in nine instances, and in 6 of these cases it could be definitely related to pressure of the tumor.

7. No endocrinologic importance could be attached to these tumors. Five cases of abnormal vaginal bleeding were adequately explained by associated pelvic pathologic conditions.

8. The most striking clinical feature was the age of the patients. In a total of 31 tumors of this distinct group collected from the literature and including this series 29 (93.5 per cent) were forty years of age or over and 20 (64.5 per cent) were fifty years of age or over.

9. Malignancy (clinically or microscopically) was not observed in any of these cases, in spite of the fact that the potentialities in this respect would appear to be as great as in the serous cystadenomas and the fibromas.

10. A chart and discussion portraying the concept that these tumors are of germinal epithelial origin and emphasizing their close relationship to serous cystadenomas and papillomatous fibromas is shown.

11. It is suggested that these tumors be classified as a special type of epithelial tumor of the ovary under the subhead of serous cystadenomas, as previously suggested by Taylor.

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SEVERE POLYNEURITIS DUE TO VITAMIN B DEFICIENCY IN PREGNANCY

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IN 1932 the author reported five cases of severe polyneuritis following pernicious vomiting of pregnancy under the title of "Toxic Neuritis Complicating Pregnancy."⁸ Since that time fifteen additional cases have been observed. In those intervening years from 1932 to 1941 further studies by many investigators have proved that the condition is due to a vitamin B deficiency and can no longer be ascribed to a "toxemia developing during pregnancy."

Beriberi has long been known in the Orient and has been reported as a complication of pregnancy. In some instances the symptoms have been mild⁹ and in some others so severe as to result in death. Theobald¹⁴ suggested in 1930 that the neuritis of pregnancy was due to a vitamin B deficiency, because the neuritic form of beriberi in Bangkok was much higher in the pregnant woman than in the nonpregnant woman, and because the symptoms of beriberi are indistinguishable from the polyneuritis of pregnancy. Some authors,^{2, 5, 7, 10, 18} however, believe that the lack of only vitamin B₁ will not cause the nervous lesions of degeneration and suggest that a deficiency of vitamin A or of other factors of the vitamin B complex is also necessary.

The deficiency of vitamin B₁ may arise from numerous factors: inadequate intake, inadequate absorption, or increased utilization, such as occurs in prolonged illness, in acute febrile conditions, or in pregnancy.

Many diets are inadequate as to vitamin B₁ content. Various investigators^{1, 4} state that in the nonpregnant individual the diet should contain 150 to 250 units per day.

The onset of a pregnancy increases the requirement of vitamin B₁, and most authors state that the intake should be doubled during pregnancy and again increased during lactation.^{4, 13, 17}

Williams, Griffith, and Fralin¹⁷ studied the vitamin B₁ intake in the diet of 91 pregnant women, using approximately 500 units as the adequate intake level per day. On this basis only 37.17 per cent of their patients had an adequate intake.

Horwitz and Farley⁶ studied 100 women estimating the O.B.T. principle in the urine and reported on 86 cases. Thirteen women had a low level; hence 15 per cent had a low intake of vitamin B.

Stahler¹² estimated the amount of vitamin excreted in the urine after daily administration of 10 mg. of thiamin intramuscularly for four days. Of the 40 mg. given, the normal nonpregnant woman excreted 46 per cent, the normal pregnant woman 30 per cent, and the polyneuritic woman 11 per cent. The polyneuritic pregnant woman retained more of the vitamin because there was a lack of it in the tissues.

The severe cases of polyneuritis with which this paper is primarily concerned develop early in pregnancy, and are usually preceded by a severe pernicious vomiting of pregnancy. Some cases have been reported in which vomiting did not occur. The deficiency of vitamin B₁ in pernicious vomiting is brought about first by a lack of food intake, second by a failure of retention of food ingested, and third by a high carbohydrate diet accompanied by administration of large amounts of intravenous glucose.

The usual history is one of vomiting with attempts at high carbohydrate ingestion and the administration of glucose, with or without improvement of the patient and the onset of a peripheral neuritis. The first symptoms are those of generalized weakness, pain in the calves of the lower legs, numbness, and tingling of the hands and feet, and inability to walk. Careful examination at this time reveals atrophy of muscles and overlying skin, and diminished or absent reflexes in the involved areas. The weakness and paralysis ascends the body. Retention of urine or incontinence with overflow, constipation, paralysis of the abdominal muscles, paralysis of the accessory muscles of the chest, and involvement of the bulbar area with diaphragmatic paralysis, tachycardia, difficulty with phonation and deglutition occur in order. Mental confusion of the Korsakoff type is frequently present.

CASE 1.—(No. 32497, University Hospital.) The patient, aged 26 years, was admitted July 24, 1930, to the Neurological Service. Patient had a regular menses July 1, 1929, and about Sept. 1, 1929, began to have nausea and vomiting for which she was treated. She improved slightly but was required to stay in bed. About December 1 she began to have severe pains in the legs with numbness and tingling. Because of continuation of the nausea, vomiting, and leg pains, a therapeutic abortion was performed on Dec. 27, 1929. The patient was unable to get out of bed until March, 1930. On admission she was wearing braces on both feet and required crutches for walking or standing.

The general physical examination was essentially negative except for the local findings of the lower extremities. This revealed a bilateral foot drop, tenderness over both achilles tendons, deep pressure pain over the calf muscles, and reversal and adduction of knees.

Patient was given massage and electrical stimulation and was dismissed Aug. 18, 1930, at her own request. There has been no known follow-up.

CASE 2.—(Methodist Hospital, service of Dr. W. H. Taylor.) Mrs. M. C., white, married, aged 27 years, para ii, gravida iii. The last regu-

lar period began May 15, 1926. At the fifth month there was nausea and vomiting. After two months of vomiting, there developed muscular weakness, areas of anesthesia of the extremities, and cramps in the legs, and signs of a pre-eclampsia, Grade II. Because of failure of conservative therapy and disappearance of fetal heart tones, a medical induction was done. The patient died twenty-four hours after delivery, the death being due to polyneuritis rather than the toxemia. No vitamin therapy was given.

CASE 3.—(Methodist Hospital, service of Dr. W. H. Taylor.) Mrs. L. H., white, married, aged 36 years, para i, gravida iii. The last regular period began Jan. 4, 1933. Nausea and vomiting began Feb. 23, 1933, and persisted in spite of dietary regulations and sedation. On April 24, 1933, she developed pain along the left supraorbital nerve, and in eight days there was ptosis of both eyelids, bilateral facial paralysis, weakness of extremities, muscular cramps, paralysis of the diaphragm, evidence of bulbar paralysis, mental confusion, and retrobulbar optic neuritis. She was given vitamin B therapy, but because of failure of therapy a vaginal hysterotomy was done. For a few days there was no change in the patient's condition, then there was slow improvement with eventual recovery in six months. (Criticism: Vitamin therapy of forty-eight hours' duration was insufficient and not a fair trial.)

CASE 4.—(No. 45620, Immanuel Hospital.) Patient, white, aged 22 years, gravida i, last period Jan. 7, 1933, developed nausea and vomiting about the middle of February, which became severe about April 12. She was treated conservatively with sedation and intravenous glucose, and improved considerably but noted some tingling of the fingers. After one week there was a recurrence of vomiting and the development of a polyneuritis which followed a rapidly progressive course of the ascending type. She died four hours after a vaginal hysterotomy. No vitamin B therapy was given.

CASE 5.—(No. 47937, University Hospital.) Patient, white, married, aged 24 years, primigravida, last period in March, 1934, had marked nausea and vomiting with the development of a typical vitamin B deficiency including polyneuritis. She aborted spontaneously Aug. 15, 1934, and was seen by the author four days later. On admission there were the typical signs of vitamin B deficiency, including polyneuritis and a Korsakoff psychosis. She received intravenous fluids as well as brewers' yeast and liver extract intramuscularly. She slowly improved, being dismissed from the hospital thirty days after her admission and was completely recovered one year later.

CASE 6.—(Methodist Hospital, service of Dr. W. H. Taylor.) Mrs. P., married, white, aged 24 years, primigravida. Her last period occurred Aug. 9, 1934. This was followed by some nausea and vomiting for two months. At the fourth month she developed a left supraorbital neuritis, paralysis of the left facial nerve and a general polyneuritis. Under treatment with vitamin B, liver extract and iron she gradually improved. She was delivered by cesarean section at term because of cephalopelvic disproportion. The baby weighed seven and three-fourths pounds. The patient made a complete recovery.

CASE 7.—(No. 53038, Immanuel Hospital.) Mrs. A., married, gravida i, white, aged 20 years, was admitted May 17, 1935. The patient had her last normal period on May 1, 1935. She had some nausea and vomiting which was mild at first and then became severe about May 1.

On hospitalization she was found to be slightly dehydrated. She was treated with intravenous glucose and rectal feedings, and after temporary improvement, she had a resumption of vomiting associated with a pulse rate of 100 to 110, hyperactive reflexes, tenderness in extensor muscles of the lower legs, and numbness and tingling in hands and feet.

She was seen in consultation and, because of the above findings, a therapeutic abortion was done May 25, 1935. She made an uneventful recovery and was dismissed on May 31, 1935, receiving four brewers' yeast tablets daily, and a high vitamin diet.

She had a normal period Nov. 25, 1936. She was seen on Jan. 14, 1937, and a diagnosis of pregnancy was made. She was given brewers' yeast tablets, three daily, and had only one or two attacks of nausea. She was delivered on Sept. 5, 1937, of a normal female child weighing 8 pounds.

CASE 8.—(No. 54244, University Hospital.) Patient, para 0, gravida i, aged 22 years, was admitted July 24, 1936. Last normal period occurred in November, 1935. There was some nausea during early weeks of pregnancy, but severe vomiting began in February, 1936. She was admitted to a hospital, given "hypos and food by vein" and after eleven weeks was dismissed improved. After several weeks she relapsed and was admitted to another hospital and then transferred to the University Hospital. She had lost 65 pounds in weight, was mentally dull, and physically weak.

Neurologic examination showed generalized muscle weakness, all types of sensation essentially normal except at the very peripheral portions, and reflexes normal except for absent knee and ankle jerks, bilateral.

A mild secondary anemia was present. She was treated with vitamin B complex, iron, and a high vitamin diet.

The patient improved rapidly and was dismissed Aug. 25, 1936, but readmitted August 30, in labor, and after normal labor delivered a normal female child, weighing four pounds one ounce. The puerperium was normal and she was dismissed on Sept. 9, 1936, completely recovered.

CASE 9.—(No. 58999, University Hospital.) Patient, colored, para 0, gravida iii, aged 28 years, was admitted Nov. 29, 1937. Last menstrual period Aug. 6, 1937. She began to have vomiting about Sept. 30, 1937. At first vomiting mild, but rapidly became severe and she was admitted to a hospital where she was treated with hypos and intravenous fluids. She was dismissed from that hospital Nov. 19, 1937, at which time she was improved except for the onset of double vision. After her dismissal she continued to vomit, complained of general weakness, pain in the legs, and tenderness to touch in the legs. Three days before admission patient became mentally confused and passed into unconsciousness. For twenty-four hours before admission there was some vaginal bleeding.

Examination on admission showed a well-developed, dehydrated, colored female, in coma; all muscles were weak, flaccid, and all reflexes hyperactive. Patient was given a blood transfusion of 500 c.c., and 500

e.c. of 25 per cent dextrose solution. She failed rapidly and died twelve hours after admission.

Autopsy: Bronchopneumonia, pregnancy, acute degeneration of myelin sheaths of peripheral nerves.

CASE 10.—(No. 62853, University Hospital.) Patient aged 27 years, para iii, gravida iv, admitted Dec. 29, 1938. Last menses occurred in August, 1938. About Nov. 1, 1938, she began to have morning vomiting. Two weeks later she reported that she tired easily and wanted to sleep a great deal. From the middle of November until December 1, she vomited constantly. Although vomiting ceased, she had extreme anorexia and ate practically nothing. One week prior to admission she became irrational. Examination revealed a well-developed, well-nourished female, talking incoherently, skin very dry, pulse rate 160; there was tenderness over the muscles of the lower extremities to pressure; reflexes were normal except for absent knee and ankle jerks. Temperature was 102° F. She was given a high caloric, high vitamin diet, at first being fed by nasal catheter. This latter method was discontinued after one week when patient took food well. She was given thiamin chloride, 18 mg. daily, and nicotinic acid, 100 mg. daily. Her hemoglobin was 40 per cent, so she was given a transfusion of 500 c.c. of citrated blood. After two weeks molded plastic splints were placed to prevent foot drop and the dosage of thiamin chloride was increased to 80 mg. daily. In spite of this, mental confusion continued, and the patient complained of extreme pain in the lower extremities. By Feb. 1, 1939, the patient was clear mentally, but there was some foot drop. The dose of thiamin chloride was reduced to 15 mg. daily, the nicotinic acid to 40 mg. daily. Oleum percomorphum to 60 drops daily, and ferrous sulfate to 12 gr. daily were added.

Improvement was steady and slow, and the patient was dismissed on March 9, 1939. She was delivered at term of a normal child. Recovery was slow but complete one year after delivery.

CASE 11.—(No. 63941, University Hospital.) The patient, white, aged 30 years, was delivered September 17, 1938, of a premature child which survived. The puerperium was complicated by the development of a paralysis of the right serratus anterior muscle, thought to be due to a vitamin deficiency. Recovery was slow in spite of a diet reinforced with vitamin B.

Patient menstruated beginning Dec. 12, 1938. She had slight nausea but rapidly developed signs of a polyneuritis in a mild form. In spite of therapy (15 mg. thiamin chloride a day), the patient failed to improve and a vaginal hysterotomy was done May 9, 1939. Improvement began within a week, and complete recovery occurred in two months.

Criticism: Therapy was insufficient as to dosage and more B fractions were given.

CASE 12.—(No. 66277, University Hospital.) Patient, aged 26 years, gravida i, was admitted July 29, 1939. The last menses began April 26, 1939. Nausea and vomiting began the middle of May and increased in severity, and then decreased about July 1. She developed polyneuritis with blurring of vision and mental confusion. These findings and a secondary anemia were present on admission. She was given a

high vitamin diet, several blood transfusions, and 20 mg. of thiamin chloride daily with brewers' yeast. She gradually improved and was delivered Jan. 4, 1940, of a normal baby after a normal labor. Lactation was insufficient. Recovery was complete by June, 1940.

CASE 13.—(No. 67303, University Hospital.) Patient, aged 30 years, para ii, gravida iii, was admitted April 6, 1940. Patient's last menstrual period occurred on July 5, 1939. Vomiting began in August and continued until the latter part of December. In the early part of December she began to have soreness in her muscles, and on December 7 she became paralyzed in her lower extremities and had been confined to her bed since. She was seen by a physician in the latter part of December. He recognized the condition as one of polyneuritis. He treated the nausea, and placed her on a regime of a high vitamin diet with thiamin chloride, 10,000 units weekly. She made a slow convalescence and on admission to the hospital was in excellent physical condition. The only abnormal findings of note were wasting of the muscles of the legs, tenderness of the muscles of the calf of both legs, and inability to walk unassisted. Reflexes were diminished in the lower extremities.

Normal onset of labor occurred on April 8, 1940, resulting in a spontaneous delivery of a normal male child, weighing 7 pounds 10 ounces. Convalescence was normal.

Treatment during stay in hospital consisted of brewers' yeast tablets (Meads) 45 tablets daily; thiamin chloride, 15 mg. daily; oleum percomorphum drops, 40 daily.

CASE 14.—(No. 68191, University Hospital.) Patient, aged 31 years, para iii, gravida iv, entered the hospital July 6, 1940. She had been in reasonably good health until July 2 when, after some exertion, she collapsed and had to go to bed. On July 4 she began to have generalized aches and pains, some nausea and vomiting and on July 6 she noted dimness of vision.

During pregnancy the diet had consisted of pork meat, canned and dried fruits and vegetables but with little or no milk or fresh fruit or vegetables. On examination a typical polyneuritis was present as well as a secondary anemia. She was placed on a high vitamin diet, 132 mg. of thiamin chloride and 300 mg. of nicotinic acid daily. She recovered rapidly and was delivered of a normal child on Sept. 16, 1940.

CASE 15.—(No. 68376, University Hospital.) Patient, aged 28 years, para ii, gravida iv, entered the hospital April 25, 1940. The last menses began Oct. 26, 1939. The patient began to have nausea and vomiting shortly after her last period, and it became so severe that she was hospitalized from December 8 to 18, inclusive, during which time she was given the usual intravenous glucose-saline solutions and little or nothing by mouth. After her dismissal, she continued to have vomiting of a less severe type until March 1, 1940. About April 10 the patient noticed blurring of vision, edema of hands and feet, headaches, and numbness of extremities.

Examination revealed a well-developed, well-nourished female. The teeth were badly decayed. A few fissures appeared at the corners of the lips. A pregnancy of approximately six months' duration was

present. The skin was dry and sealy over the elbows and the shins. There was some edema of the hands and the feet.

Hemoglobin was 75 per cent; basal metabolism, 7 per cent. Urine showed nothing abnormal.

She was placed on a high vitamin, high calorie diet with addition of thiamin ehloride, 10 mg. daily. Brewers' yeast, 60 tablets daily, was given with thyroid, gr. $\frac{1}{2}$ twice daily.

Neurologic examination was essentially normal.

She was dismissed greatly improved on May 10, 1940. The patient was readmitted on July 24, 1940, with membranes ruptured but no pains. After forty-eight hours, she was given castor oil and quinine induction. Labor lasted two and one-half hours, and she was delivered of a normal male ehild. The puerperium was normal and the patient was dismissed Aug. 5, 1940.

In the main the histories and physical findings follow the typical eases previously reported. One notes, however, the frequency of ocular symptoms. Three patients complained of blurring of vision, and in one patient there was retrobulbar optie neuritis. This is an incidence of 26.6 per cent of ocular symptoms. No previous reports have carried such a high incidence.

The reports of 130 eases (19 to 59) of severe polyneuritis in the literature were reviewed, and with the 15 eases herein reported, a total of 145 eases are available for study. Some of the protocols are incomplete in all details and not all of the eases can be included.

One hundred and five patients received no vitamin B complex or vitamin B₁ therapy. Forty patients were treated with varying amounts and varying fractions of the vitamin B complex.

In the total series there were 40 deaths, or a mortality of 27.5 per cent. Thirty-seven of the deaths occurred in the 105 patients receiving no vitamin B complex therapy, an incidence of 35.2 per cent, while only 3 of the 40 patients receiving vitamin B complex therapy died, an incidence of 7.5 per cent.

The termination of pregnancy in 131 cases was studied¹⁹⁻⁵⁹ and recorded in Table I.

TABLE I

TYPE OF DELIVERY	TOTAL SERIES			NO VITAMIN THERAPY			VITAMIN THERAPY		
	NO.	DIED	%	NO.	DIED	%	NO.	DIED	%
Abortion, induced	62	19	28.3	53	17	32.0	9	2	22.2
Abortion, spontaneous	13	2	15.3	8	1	12.5	5	1	20.0
Term (viability)	47	2	4.2	21	2	9.5	26	0	
Died undelivered	9	9	100.0	9	9	100.0			
(previable)									
Still pregnant	1			1				0	
Unrecorded termination	13	8	61.5	13	8	61.5			
Total	145	40	27.5	105	37	35.2	40	3	7.5

A study of this table reveals some interesting facts. When pregnancy was terminated in the previable period the mortality rate was 28.3 per cent. In the patients receiving no vitamin therapy, the rate was 32 per cent and in the vitamin therapy series 22.2 per cent, the difference being practically negligible and indicating that abortion was perhaps done too soon in the latter series or that therapy was incomplete. When abortion was spontaneous, the mortality rate was 15.3 per cent in all cases, and 12.5 per cent and 20 per cent, respectively, in the nontreated and treated group. Here again, though the series is small, there is little or no difference, but definitely the mortality rate is lower than in the group of artificially terminated pregnancies.

In the 47 patients going to term, only two died, an incidence of 4.2 per cent, and both of them were in the nontreated group. Twenty-six patients received vitamin therapy and went to term with no fatalities in the group.

Early and effective therapy then is indicated and interruption of pregnancy is not indicated. From a study of the literature and from a careful review of a personal series, it is an opinion that interruption of pregnancy is definitely contraindicated, is fraught with danger, and is definitely a factor in the production of a higher mortality rate.

In an effort to determine what constitutes adequate therapy, the forty patients receiving vitamin therapy were studied. No uniform dosage or combination of various fractions of the vitamin complex or of other vitamin was used. That a large dosage of thiamin chloride is indicated is demonstrated by reviewing the personal series. The average daily dose of thiamin chloride in five cases was from 10 to 18 mg.; in Case 10, 80 mg. per day; and in Case 14, 132 mg. per day for seventeen days.

Matsen⁴⁷ and Behrman²⁰ both recommend 20 to 50 mg. of thiamin chloride daily, for at least two weeks. No harmful effect was noted from these larger dosages. Unfortunately no studies of excretion were done, so that the actual utilization of such large dosages cannot be ascertained. A clue as to the amount of thiamin chloride required daily is given in a recent case (U. H. 73607) of pernicious vomiting seen at the third month of pregnancy. The patient had all the typical signs and symptoms of a combined pellagra and scurvy without evidences of a polyneuritis. The blood pyruvic acid on admission was 3.7 mg. per cent, and although the patient was given 100 mg. of thiamin chloride daily, the pyruvic acid level did not reach 1.2 mg. per cent until the eighth day of therapy. The level then varied from 1.6 to 2.1 mg. per cent on a daily intake of 100 mg. thiamin chloride.

It seems reasonable that 10 to 15 mg. of thiamin chloride daily is a sub-minimal dose in these cases and that 50 to 100 mg. per day is necessary. This must, however, be reinforced with a diet high in other vitamins and

B complex as soon as the patient is able to take food. In some instances the addition of hydrochloric acid to promote digestion, and of an iron compound to combat anemia is necessary.

Passive motion of paralyzed extremities and proper splinting to combat deformities must also be done. The rate of recovery is slow. Improvement may be noted within a week but many patients do not regain full usage of the involved muscles until six to fifteen months have elapsed after the onset of therapy. This is emphasized in 40 cases in which the rate of recovery is mentioned. The recovery rate in months was not given in many instances but stated as "slow" or "long recovery." When the recovery rate was given it varied from two months to eighteen months, the average being 7.5 months.

Every patient who has nausea and vomiting should receive at least 1,000 units of thiamin chloride, and an adequate amount of B complex daily, taken at a time when the vomiting is least likely to occur. If this cannot be taken and retained orally then corresponding amounts should be given intramuscularly. This will prevent the appearance of the early signs of vitamin B deficiency, one of which is vomiting, and the development of polyneuritis which is a late sign of polyvitamin deficiency.

No definite conclusion has been reached as to the effect of vitamin B deficiency upon the fetus in utero. Intrauterine death does occur, and spontaneous abortion is not infrequent.

Uneo,¹⁵ and Moore and Brodie¹¹ fed rats on a vitamin B deficient diet and noted abortions and absorption of the embryo, death of the young at birth or during the nursing period. The animals exhibited all the evidences of severe polyneuritis, and on autopsy there was found myelin degeneration of the phrenic and vagus nerves. Moore and Brodie report the case of a woman on a deficient diet who had a normal delivery and a post-partum hemorrhage. Although the baby appeared normal, it developed hemorrhages in the urine, became jaundiced, and died on the fifth day. Autopsy revealed many hemorrhagic areas, dilatation and hypertrophy of the right ventricle of the heart and myelin degeneration in the nerves. Careful examination of the 145 cases herein studied or reported failed to reveal post-mortem examinations of the fetus at any stage of gestation. This should be done in the future, for further study on this problem is necessary.

Vignes¹⁶ regards vitamin B deficiency as frequently responsible for abortion, and ineffectual labors with post-partum hemorrhage and inertia uteri.

In the 26 women in the present study who received vitamin therapy, there was no recorded incidence of inertia uteri or post-partum hemorrhage. One infant was macerated at birth, all others were apparently normal infants. In the 21 women who continued the pregnancy to the period of viability, or to term without vitamin therapy, two were delivered by abdominal cesarean section, one by vaginal cesarean section,

and the remainder had normal deliveries, without any recorded evidence of inertia uteri or hemorrhage. The babies were all said to be normal living children.

There is insufficient evidence present in the protocols of the 47 women to make any statement as to the effect of the vitamin deficiency or vitamin therapy on lactation.

Stahler¹² estimated the amount of vitamin B₁ in the blood of four newborn children and found meager amounts of vitamin B₁ in the umbilical cord blood unless the mother received 10 mg. of vitamin B₁ shortly before delivery. The placenta, then, prevents no barrier to the passage of the thiamin from mother to child. Whether it also acts as a storehouse or reservoir is unknown. Dubrausky and Lajos³ found the vitamin B₁ level of the placenta higher than either the maternal or fetal blood levels. From their unconfirmed investigation it would appear that the placenta could act as a reservoir, giving the intrauterine fetus protection for a longer period of time in instances of maternal deficiency.

SUMMARY

1. Pernicious vomiting of pregnancy may result in a vitamin B deficiency with a severe polyneuritic syndrome.
2. Ocular symptoms which heretofore have not been stressed were present in 4 of 15 cases.
3. One hundred and thirty previously reported cases are reviewed with respect to vitamin therapy and maternal mortality, and 15 additional cases are reported.
4. If a polyneuritis develops 50 to 100 mg. of thiamin chloride should be given daily. No complications from these large doses have been observed.
5. Therapeutic abortion is definitely contraindicated, and if done increases the mortality rate.
6. Ultimate recovery is slow under the best of therapy and may require fifteen to eighteen months.
7. Further study is necessary to determine the effect of vitamin B deficiency on the fetus in utero in the human being. The same statement holds true in regard to the placenta.

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ETHER IN THE BLOOD OF THE NEWBORN INFANT

A QUANTITATIVE STUDY

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OBSTETRIC anesthesia may disturb the onset of respiration at birth by producing either (a) anoxia, or (b) anesthesia, or (c) both of these states. Thus, on the one hand (a), the oxygen supply of the mother's blood may be affected so as to diminish the amount of oxygen available to the fetus during the last critical moments when it is still dependent upon the placental circulation. Under such circumstances the infant may be born with the nervous control of respiration temporarily or permanently damaged by anoxia. Evidence has been put forward by various authors¹⁻³ to show that the onset of neonatal respiration may be disturbed in this way by the use of too much nitrous oxide gas, and perhaps during the administration of other anesthetic agents. On the other hand, (b) as might be expected, some anesthetic substances may themselves pass through the placenta and accumulate in the fetal blood in concentrations sufficient to render respiration shallow or delayed at birth from actual narcosis, despite adequate fetal blood oxygen levels. There are probably situations, (c) in which both the former and the latter disturbances affect the baby, but we have felt that delayed respiration or apnea, due entirely to the directly narcotizing effect of the anesthetic, was primarily the mechanism involved when babies were slow to breathe after delivery under ether. Although Eastman¹ found that in eight infants so delivered, the blood oxygenation was slightly below that expected in deliveries without anesthesia, a similar comparison in a somewhat larger series⁴ showed the oxygen levels of babies delivered during ether anesthesia to be somewhat higher than the levels in the unanesthetized controls. Moreover the infants of this series who displayed some degree of apnea were not worse off for oxygen than were the others who breathed promptly.

In earlier papers the average amounts of nitrous oxide and of cyclopropane⁴ in the maternal and the fetal blood at birth have been stated, but no figures have been found in the literature to indicate how much ether may enter the blood during the average delivery and how this is distributed between the maternal and fetal circulations. Because of this gap in our knowledge, and because we have reason to believe that any neonatal respiratory difficulty *assignable to the anesthetic* in deliveries under ether is usually a narcotic and not an anoxic phenomenon, it

seemed important to measure the amounts of ether actually present in the blood of the mother and of the infant in a considerable series of unselected deliveries.

METHODS

As soon as the infant was born, a section of the umbilical cord was isolated between two clamps. The contents of the umbilical vein and of the umbilical arteries in this isolated section thus represented the fetal arterial blood as it flowed from the placenta to the infant and the fetal venous blood returning to the placenta to be re-oxygenated; the isolation of this cord segment supposedly preserved these samples in the state obtaining immediately after birth. As soon as this length of cord could be removed to the laboratory, a sample was drawn from the umbilical vein, and from the arteries also if they contained sufficient blood. These samples were drawn into glass syringes in which oxalate, or heparin, and mercury were used to fill the dead space, as suggested by Adriani.⁵ In many instances a specimen of venous blood was taken from the mother's arm at the exact time the cord specimen was isolated, or as near it as possible.

For a considerable period of time we attempted to use the iodine-pentoxide method of Haggard⁶ for the determination of ether in blood. This procedure proved unreliable in our hands, however, and we therefore gave it up in favor of the sulfuric acid dichromate method of Shaffer and Ronzoni.⁷

Clean outside air is slowly drawn over a 2 c.c. sample of the blood to be tested, thus vaporizing its ether content. This air is then bubbled slowly through 5 c.c. of concentrated sulfuric acid with the formation of ethyl sulfuric acid. The vaporization requires about two hours, and during the last half hour of this time the blood sample is immersed in a warm water bath to volatilize the last trace of ether. A measured amount of a standard bichromate solution is pipetted into the acid, the tubes being immersed in running tap water to prevent heating. The acid bichromate is then allowed to stand overnight to insure complete oxidation. An excess (2 to 4 Gm.) of potassium iodide is added with starch solution as an indicator. The liberated iodine is titrated against standard thiosulfate solution and the ether content of the 2 c.c. blood sample determined by a simple calculation. Repeated analyses for known amounts of ether added to blood have shown an accuracy, in our hands, of about 96 per cent for this method, as indicated by the results of trial assays in Table I.

TABLE I. ACCURACY OF METHOD. AMOUNT OF ETHER RECOVERABLE FROM SAMPLES OF KNOWN COMPOSITION

ETHER IN SAMPLE	ETHER RECOVERED		AVERAGE	PERCENTAGE
	TRIAL 1	TRIAL 2		
1. 2.13 Gm./liter	2.04	2.06	2.05	96.4
2. 3.40 Gm./liter	3.41	3.31	3.36	98.8
3. 7.71 Gm./liter	7.60	7.24	7.42	96.2

Since the placenta is a highly permeable barrier and should be particularly so for such volatile substances as ether no great difference was expected between the level of ether in the blood of a mother and in that

of her baby before the onset of neonatal respiration, although some individual variations were anticipated. Therefore, in the beginning of this work, it was puzzling to find the quantity of ether in the blood from the umbilical vein often considerably less than that in a specimen taken from the maternal vein at the moment when the cord was clamped. An explanation appeared when, at the suggestion of Dr. Charles C. Roby, we investigated the diffusion of ether through the walls of the umbilical vessels to the surrounding atmosphere during the few minutes elapsing from the time the cord was clamped until the time syringes were filled from its vessels in the laboratory. Since for various reasons it seemed wiser to use a collection process which necessitated this short interval, and since it was found that diffusion (with consequent lowering of the ether level in the cord vessels) did actually occur, a correction factor was devised. This was accomplished by measuring the ether in the vessels of umbilical cords obtained repeatedly from the same vessels at five-, ten-, and fifteen-minute intervals after the delivery. From the averages of such data, it was possible to project a curve for ether loss through the wall of the umbilical vein and a corresponding one for the umbilical arteries; reference to this curve and to the time elapsed between clamping the cord and sampling its contents allowed a reasonably accurate measurement of the original ether values by adding the resultant correction factor to the actual amount of ether in the sample. No such correction was needed for the maternal vein specimens, since they were drawn directly from the arm into the storage syringe. It was interesting that the correction factor for blood standing in the thin-walled umbilical vein proved to be larger (0.15 Gm. per liter of blood during five minutes) than that for blood in the thicker-walled arteries (0.12 Gm. for the same period). While delay in removing specimens from the vessels into the syringes did cause this predictable and correctable loss, it was found by repeated trials that once in the syringe the blood sample could be stored several hours, or overnight, if necessary, with only insignificant alterations in the amount of ether recoverable. Such a storage period was seldom required, as it was usually possible to collect the blood during the morning and to begin the chemical analyses immediately.

RESULTS

A general tabulation of the results from 68 infants and 58 mothers is presented in Table II. This enumerates a series of 66 deliveries (two with twins), in all of which at least one sample of cord blood, usually from the umbilical vein, was secured. At the majority of deliveries, a specimen from the maternal vein was also obtained; in somewhat less than one-half an umbilical artery specimen was available. In 22 deliveries with 23 infants, all three specimens were secured. The figures of Table II are perhaps more easily comprehended if spotted on a chart (Fig. 1), which shows the range over which the data spread, although it does not identify those maternal and fetal bloods which were obtained at the same delivery.

Several facts are apparent. The amounts of ether in the maternal venous and the umbilical vein (actually fetal arterial) bloods are scat-

TABLE II. ETHER, IN GRAMS PER LITER, IN MATERNAL AND FETAL BLOOD AT DELIVERY

TYPE OF DELIVERY†	ANESTHETIC			ONSET OF RESPIRATION*	UMBILICAL VEIN	UMBILICAL ARTERY
	TYPE	DURATION (MINUTES)	MATERNAL BLOOD			
1 N.D.	Closed		0.658	B	0.633	0.443
2 N.D.	Closed	25	0.724	A	0.789	0.489
3 L.F.	Closed	15	1.084	A	0.689	0.480
4 N.D.	Closed	12	0.667	A	0.744	0.489
5 N.D.	Closed		0.528	A	0.492	0.156
6 N.D.	Closed	16	0.848	A	0.743	0.610
7 L.F.	Closed	14	0.324	A	0.418	0.239
8 N.D.	Open	17	0.594	B	0.538	0.480
9 L.F.	Closed	20	0.658	A	0.585	0.378
10 N.D.	Closed	20	0.545	A-	0.510	0.000
11 L.F.	Closed	26	0.937	A	0.790	0.295
12 N.D.	Closed	22	0.722	A	0.538	0.220
13 N.D.	Closed	35	0.851	A	0.705	0.324
14 L.F.	Closed	35	0.927	A	0.970	0.656
15 N.D.	Closed		0.895	B-	1.030	0.439
16 L.F.	Open	50	0.556	B	0.558	0.371
17 L.F.	Closed		0.787	B	0.481	0.378
18 N.D.	Closed		0.292	A	0.603	0.423
19 N.D.)	Closed		0.949	C	1.104	0.360
20 twins N.D.)	Closed			Case 1 C	1.492	0.462
				Case 2		
21 L.F.	Open	23	0.292	A	0.603	0.463
22 N.D.	Closed	10	0.445	A-	0.488	0.248
23 L.F.	Closed		1.084	A	0.705	0.564
Average of 22:			0.698	Average of 23: 0.704		0.389
24 N.D.	Open		0.650	A	0.690	
25 N.D.	Open		0.844	A	0.706	
26 N.D.	Open		0.496	B	0.520	
27 N.D.	Closed		1.011	A	0.511	
28 N.D.	Closed		0.835	A	0.835	
29 N.D.	Closed		0.631	A	0.595	
30 N.D.	Closed		0.733	A	0.695	
31 L.F.	Closed		0.454	B	0.414	
32 L.F.	Closed	25	0.909	A	0.687	
33 N.D.	Closed	8	0.468	A	0.492	
34 N.D.	Open		0.786	A	0.873	
35 L.F.	Open		0.900	A	0.900	
36 N.D.	Closed	25	0.602	A	0.536	
37 N.D.	Open		0.528	A	0.492	
38 N.D.	Closed	19	0.742	A	0.797	
39 N.D.	Open		0.519	A	0.511	
40 N.D.	Closed	14	0.787	A	0.659	
41 N.D.	Closed	25	0.334	A	0.456	
42 N.D.	Closed	24	0.845	C	1.140	
43 Br.	Closed	20	0.897	B	0.880	
44 L.F.	Closed	27	0.482	C	0.660	
45 L.F.	Closed	20	2.030	C	1.143	
46 N.D.	Closed		0.555	A	0.511	
47 M.R.	Closed	20	0.900	C	0.790	
48 N.D.	Closed	20	0.437	A	0.464	
49 Br.	Closed	32	1.080	A	1.160	
50 N.D.	Closed	30	0.474	A	0.502	
51 N.D.	Closed	11	0.538	A	0.390	
52 L.F.	Closed	23	0.445	A	0.557	
53 N.D.	Closed	11	0.649	A	0.697	

*Onset of respiration: A, immediate; B, slightly delayed; C, delayed, required some resuscitation.

†Type of delivery: N.D., normal; L.F., low forceps; Br. breech; M.R., manual rotation.

TABLE II—CONT'D

TYPE OF DELIVERY†	ANESTHETIC			ONSET OF RESPIRATION*	UMBILICAL VEIN	UMBILICAL ARTERY
	TYPE	DURATION (MINUTES)	MATERNAL BLOOD			
54 M.R.	Closed	17	0.585	C	0.604	
55 N.D.	Closed		0.695	A	0.604	
56 N.D.	Open		0.343	A	0.520	
57 N.D.	Open		1.309	C	1.290	
58 L.F.	Closed		0.910	A	0.622	
Average of 57:			0.713	Average of 58: 0.692		
59 N.D.	Closed			A	0.474	0.232
60 L.F.	Closed			A	0.511	0.285
61 N.D.	Closed			A	0.233	0.298
62 N.D.	Closed			A	0.894	0.573
63 N.D.	Closed			A	0.659	0.248
64 L.F. } twins	Closed			A	1.085	0.517
65				A	Case 1 0.511	Case 1 0.000
					Case 2 0.547	Case 2 0.415
66 N.D.	Open			A	0.530	0.260
67 L.F.	Open			A	0.734	0.555
68 N.D.	Closed		A			
Average of 68:			0.681; of 33: 0.374			

tered through a wide range of values, but their averages are very nearly identical at about 0.7 Gm. of ether/liter of blood. If, as on the spot chart, the extreme 10 percentiles are not included and the zones (shaded in the chart) occupied by the middle 80 percentiles are compared, it will be seen that they closely approximate one another, with the figures on the fetal side of the placenta a little higher than those for the maternal blood. Although this suggests a close relationship constantly maintained across the placenta, such a relationship is not borne out by determinations for individual mothers and their babies. Thus, at the delivery of Patient 3, for example, the maternal value was nearly 1.1 mg., the fetal less than 0.7, while in Case 27, the fetal value was about one-half the maternal. In other instances, such as Cases 15 and 19, the fetal blood contained much more ether than the maternal. Nevertheless, the average ether level for the infants of the 10 mothers having the most ether in their blood was 0.943, while in the infants of the 10 mothers having the least ether the corresponding figure was only 0.502. The ether present in blood returning to the placenta in the umbilical arteries was represented by a more compact group of figures, below those for the umbilical vein in proportion to the amount of ether which must have been absorbed by the fetal tissues, and yet to some degree overlapping the umbilical vein levels (Fig. 1). In 32 of the 33 infants on whom umbilical vein and artery specimens were both obtained, the amount of ether was less in the latter.

The comparison between maternal and fetal ether levels suggests an unstable and frequently changing situation which, nonetheless, tends

to be fundamentally consistent. In an effort to check the effect of the varying conditions occurring during the progress of obstetric anesthesia, we examined two venous blood samples from the same woman at a five-minute interval shortly before the moment of birth. Such figures, secured from 26 patients, are shown in Table III. There was no regularity of results, so that the quantity of ether increased in the blood of 12 patients, decreased in that of 12 others, and remained the same in two. Such divergent findings, present because the patients were not saturated and thus stabilized with regard to ether, make it less surprising that the

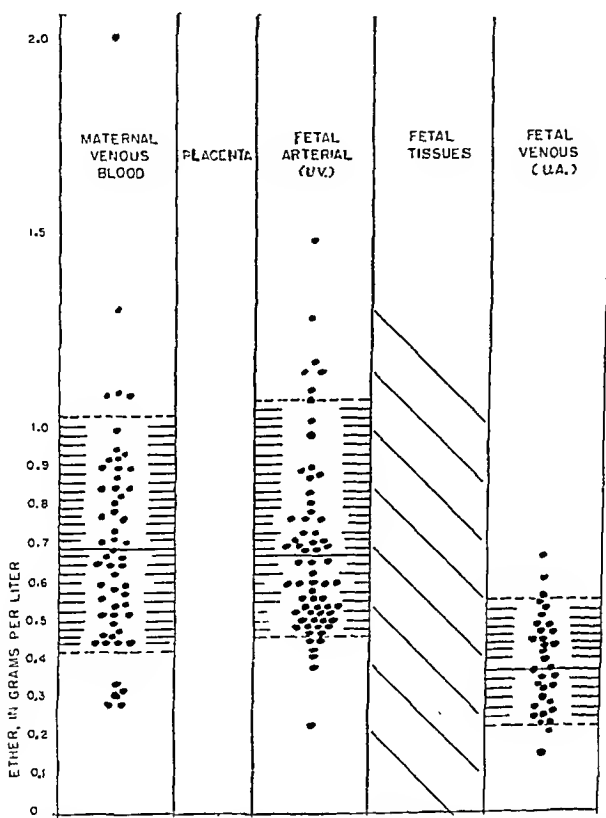


Fig. 1.—Amounts of ether in maternal and fetal blood at delivery, from the data of Table I. Each dot stands for one specimen. The solid horizontal line represents the average in each column; 80 per cent of the values fall within the shaded areas.

amounts of ether in maternal blood were so widely scattered at birth. With such variable and shifting ether values in the maternal circulation the amounts in the fetal blood might not simultaneously and exactly reflect each change on the maternal side of the placenta. Nevertheless the quantity of ether reaching the fetus in the umbilical vein was roughly proportional to that in the mother's blood. The general level lay between 0.45 and 0.90 Gm. of ether per liter of blood in samples from both these sources, nor was this influenced by the way in which the ether was administered (Table IV).

TABLE III. CHANGE IN ETHER IN MATERNAL BLOOD JUST BEFORE DELIVERY*

	TYPE OF ADMINISTRATION	ETHER IN VENOUS BLOOD	
		± 5 MINUTES BEFORE DELIVERY	AT DELIVERY
1	Closed	0.510 Gm./L	0.658 Gm./L
2	Closed	0.760	0.909
3	Open	0.909	0.786
4	Closed	0.900	0.724
5	Closed	0.620	0.580
6	Closed	0.500	0.845
7	Closed	1.204	0.897
8	Closed	0.667	0.667
9	Open	0.528	0.519
10	Closed	1.002	0.695
11	Closed	0.232	0.324
12	Closed	0.611	0.787
13	Closed	0.779	2.030
14	Closed	0.417	0.343
15	Closed	1.507	0.658
16	Closed	0.640	0.900
17	Closed	0.380	0.545
18	Closed	0.670	1.820
19	Closed	0.555	0.555
20	Closed	0.555	0.482
21	Closed	0.555	0.185
22	Closed	0.138	0.464
23	Closed	0.575	0.445
24	Closed	0.269	0.656
25	Open	0.547	0.510
26	Closed	0.796	0.910
Average 26:		0.647	0.727

*Amount of ether increased in 12.

Amount of ether decreased in 12.

Amount of ether unchanged in 2.

TABLE IV. EFFECT OF METHOD OF ADMINISTRATION AND OF PRE-ANESTHETIC RECTAL ETHER

ADMINISTRATION OF ETHER	NUMBER OF SAMPLES	SOURCE	ETHER GM./L (AVERAGE)
Open drop method	12	Maternal vein	0.651
	14	Umbilical vein	0.663
	5	Umbilical artery	0.398
Closed method	45	Maternal vein	0.732
	54	Umbilical vein	0.685
	28	Umbilical artery	0.369
Rectal ether as pre-anesthetic medication plus ether anesthesia	10	Maternal vein	0.655
	11	Umbilical vein	0.682
	8	Umbilical artery	0.411

DISCUSSION

Goodman and Gilman⁸ state that the presence of 1.0 to 1.1 Gm. ether per liter in the venous blood results in a state of light anesthesia. Most of the results in this study fell below this range, especially those for the infants, whose *venous* blood (that in the umbilical arteries) contained an average of only 0.37 Gm./liter, as against the average of 0.68 Gm. for their *arterial* blood. The significance of these figures emerges more

clearly if one reviews a few pharmacologic facts on the absorption and behavior of ether in the body. If air containing a constant percentage of ether is continuously administered to an experimental animal, the concentration of ether in the arterial blood rises more rapidly than that in the venous, the difference between the two being the amount of ether which is deposited in the tissues through which the blood has circulated. After a certain time the tissues become saturated so that no more ether can be taken up by them, then the venous and arterial levels become more or less equal. Robbins⁹ has found this state to be brought about after from thirty to sixty minutes of ether administration while Haggard¹⁰ published the protocol of an experiment in which the venous level was slightly below the arterial after as much as 120 minutes of

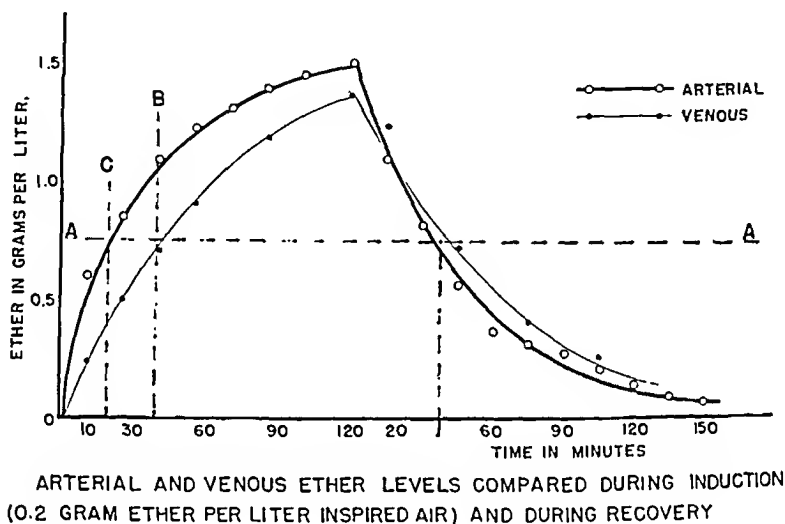


Fig. 2.—Data from experiment of Haggard presented and arranged in graphic form with his permission. The line A . . . A has been superimposed upon his data at the level of maternal venous and fetal arterial ether concentration as found in the present study. Line B indicates, in general, the maternal range; Line C, the fetal.

administration. The exact saturation point depends, obviously, on a number of factors such as the amount of ether in the respiratory mixture and the depth of breathing. After administration is stopped, elimination at once begins, with a gradient downward from the tissues via the veins to the lungs, so that while ether is being removed the amount in the veins is above that in the arteries.

This is graphically shown by the curved lines of Fig. 2, which has been prepared from Haggard's data obtained in the animal experiment mentioned above. The arterial level may be seen to be consistently above the venous until just after administration has ceased, when it falls below the venous curve. To illustrate the quantitative interrelationships of ether in the maternal and fetal bloods during delivery, certain general average figures from the present study have been indicated on the same diagram. The horizontal dotted line A . . . A is drawn at a

level of about 0.7 Gm. ether/liter, and thus indicates the amount in the venous blood of the average mother in the series. In general, one may expect that the average level in the maternal arterial blood must have been somewhere in the neighborhood of 1.1 Gm., since the vertical line *B* indicates that to have been the level in the experimental animal at the time the venous level was 0.7 Gm. At least the maternal arterial ether blood must lie above the venous. The dotted line *A . . . A* also represents the level of ether in the *arterial* blood of the fetus at birth, since such is the character of the blood coming from the placenta in the umbilical vein. If one drops another perpendicular line (*C*) on the diagram to denote an arterial level of 0.7 Gm. ether, the simultaneous venous level falls at about 0.35 Gm./L, and this agrees very well with our average figure of 0.37 Gm./L in the fetal venous (umbilical artery) specimens. In short, although it is true that ether administered to the mother reaches the fetus as well, it seems to do so at a considerably lower level. The beginnings of placental separation, or at least of impaired contact between uterus and placenta may have something to do with this relationship, and a certain amount of ether may be taken up in the amniotic fluid, as Dr. Irving¹¹ has suggested. The authors have not as yet determined how much of the ether reaching the placenta goes off in that direction and how much more may be absorbed by placental tissue itself. Any distribution of anesthetic to these regions must diminish that available for absorption by the fetal tissues. It is true, however, that just as prolonged administration tends to saturate the tissues of any subject and to bring venous and arterial levels closer to one another, so its effect in obstetrics would be to elevate the ether level in all parts of the fetus toward that of the mother, and thus to eliminate any advantage or protection accruing to the fetus in anesthesia of the usual duration. All of these statements must, of course, be made in the most general way, since cells differ in the rate at which they absorb ether, and nothing is known of the behavior of the fetal brain tissue, for example, in this regard.

TABLE V. ETHER CONCENTRATIONS IN THE VENOUS BLOOD OF MOTHERS AND THEIR INFANTS APPROXIMATELY THE SAME TIME AFTER DELIVERY

CASE	HOURS AFTER DELIVERY	GRAMS ETHER PER LITER BLOOD	
		MATERNAL VENOUS	INFANT'S VENOUS
1	1¾	0.416	0.371
2	2	0.268	0.268
3	2	0.324	0.185
4	2	0.278	0.167
5	2	0.370	0.278
6	2	0.370	0.093
7	2	0.370	0.232
8	1¾	0.000	0.362
9	1½	0.093	0.000
10	1¾	0.371	0.093
11	2½	0.000	0.000
12	2½	0.139	0.093
13	1½	0.240	0.139
14	2	0.208	0.278
15	2	0.139	0.111
16	3	0.009	0.000
Average of: 16		0.275	0.167

Some evidence has been obtained to show that after the administration of ether is stopped the fetus probably eliminates it as rapidly as does the mother. Table V shows that an hour or two after delivery samples obtained simultaneously from the mother's and the infant's veins usually show a smaller amount in the latter specimen. Whether or not an extra quantity was administered to the mother after delivery for purposes of episiotomy repair, the favorable position of the infant thus after as well as during birth is apparent from these data. The respiratory minute volume of the infant is much greater per unit of body mass than that of the mother, which gives a decided advantage to the infant in clearing a volatile anesthetic from the blood stream. It is, of course, possible that the fetus and newborn infant may respond more sensitively than the adult organism to small quantities of ether; no observations are available on this point. That the anesthesia does affect the fetus and newborn infant sufficiently to produce some sluggishness of response must be accepted, but the degree of actual hazard requires some discussion and qualification.

Every writer on neonatal apnea mentions direct anesthesia as one of several jeopardizing factors, but we have encountered only four attempts to secure quantitative measurements bearing upon the ether problem in obstetrics. Two of these, concerned largely with the oxygen relationships of ether anesthesia, have been mentioned above.^{1, 4} Another study, that of Cole, Kimball, and Daniels,¹² used the very practical and simple method of timing the interval between delivery and respiratory onset in a large series of infants, and of noting the circumstances under which important delay occurred. The evidence obtained showed that ether had a definite effect in delaying the onset or disturbing the depth of respiration after birth, and that these effects increased in severity the longer the anesthetic had been administered. A striking thing shown by Cole, Kimball, and Daniels was the large percentage of severe apnea resulting when ether had to be given for more than thirty minutes, although by contrast with deliveries under nitrous oxide the effects of ether were comparatively moderate. One must accept the general evidence presented in that study as confirming fairly frequent clinical encounters with sleepy newborn infants, smelling of ether and breathing shallowly, although with fair regularity. It should be noted, however, that this is a self-righting condition, as with every breath the infant exhales he is getting rid of his ether load, so that this sort of infant almost always has a better prognosis in the nursery than does one whose respiratory sluggishness and irregularity is the consequence of an episode of anoxia. Apnea due to anesthesia is not deleterious until after birth, by which time the administration is over and elimination begun, whereas anoxial disturbances can and do involve the fetus in utero as well as the infant after birth.

The other study of interest was made by Rosenfeld and Snyder¹³ upon fetal animals whose mothers were given various sedatives and anesthetics. The fetal movements of respiration were suppressed during

administration of most of these substances to the mother, often before surgical anesthesia was brought about in the maternal animal. This was the case in the observations with ether. The application of these studies to obstetrics and pediatrics is in some doubt until it can be shown that all fetuses including the human being make such movements normally and "physiologically," and certain questions have recently been raised upon that point.¹⁴

Our own observations agree with those just discussed in demonstrating that hesitation in respiratory onset does occur in some human infants whose mothers are anesthetized with ether and is correlated with the amount of ether reaching the fetus, which is in turn related to the amount in the maternal circulation. In Table II, the onset of respiration has been characterized by letters A, B, and C to indicate, respectively, immediate respiration, slight delay, and delay calling for resuscitation usually of a simple variety. Table VI presents the average

TABLE VI. RELATIONSHIP OF AMOUNT OF ETHER TO ONSET OF RESPIRATION

STATE OF INFANT	(A) BREATHED AT ONCE	(A-, B, C) BREATHING DELAYED	(C) REQUIRED RESUSCITATION
Maternal vein	0.684 Gm. (40)*	0.789 Gm. (17)	1.015 Gm. (7)
Umbilical vein	0.643 Gm. (50)	0.793 Gm. (18)	1.028 Gm. (8)
Umbilical artery	0.387 Gm. (23)	0.243 Gm. (9)	0.422 Gm. (2)

*Figure in parentheses represents number of samples.

figures, first in all deliveries resulting in babies breathing at once, second, in all other deliveries, and third, in the eight deliveries after which the infants required resuscitation. The increase as one passes from each of these categories to the next is very apparent as is the relationship between the maternal vein and umbilical vein averages in each group. The small number of figures for umbilical artery blood makes the averages of that group of no statistical value. Thus, while as stated at the beginning of this paper, no anoxial element is responsible for apnea in the newborn delivered under ether, there is a definite effect traceable to the anesthetic as such. Should breathing begin after only brief hesitation due to this cause, as is usually the case, the anesthetic in the infant's blood will have done no harm and will be eliminated. On the other hand, should the baby be sufficiently anesthetized so that the respiratory onset is more than slightly delayed, then the element of anoxia does become present, and increases.

Finally, before drawing conclusions, it must be emphasized that there are many other aspects by which the suitability of ether as an obstetric agent may be considered besides those described above. No attempt has been made here to discuss other factors than (1) the comparatively safe margin of oxygen supply in the obstetric use of ether, and (2) the degree to which ether itself may be expected to appear in the maternal and fetal blood during more or less routine deliveries.

CONCLUSIONS

1. In a series of 68 deliveries, the concentration of ether in blood from the umbilical vein was 0.681 Gm. per liter. The average in the venous blood of the mothers of 58 of these infants was 0.713 Gm. per liter. In 33 infants the umbilical arteries contained blood with an average ether content of 0.374 Gm. per liter.

2. The relationship between maternal and fetal ether levels was generally, although not always individually, a directly proportional one.

3. The low amounts in the umbilical artery blood suggest that the fetal tissues receive less ether than do the maternal.

4. Maternal and fetal ether levels were not influenced consistently by the type of administration nor by the use of rectal ether as a pre-anesthetic medication.

5. The blood of infants breathing at once, and that of their mothers, contained considerably less ether than did that of infants and mothers at deliveries associated with neonatal apnea.

6. Thus, ether administered to the mother during delivery may produce delay in the onset of respiration in the newborn infant. Ordinarily, this is not due to interference with the maternal and fetal oxygen supply but to the presence of ether in the fetal blood and tissues.

7. The comparatively large minute volume of respiration in newborn infants favors the rapid elimination of ether.

8. The relationship between apnea due to anesthesia and that due to anoxia is briefly discussed.

The analyses were done by Miss Virginia Nasman. The assistance of Dr. Henry Beecher and of Dr. F. C. Irving and the Staff of the Boston Lying-in Hospital is very gratefully acknowledged.

While this paper was in press, a communication appeared from Potter and others,¹⁵ presenting figures for the amounts of ether in the venous blood of patients under that anesthetic. The averages ranged from 0.87 to 1.13 Gm./L. in various groups of patients.

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THE USE OF ERGONOVINE IN THE PLACENTAL STAGE OF LABOR*

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THE third stage of labor is probably the most important phase of parturition. Notwithstanding the fact that it occupies an insignificant period of time in the many hours devoted to labor, this short period is packed with many hazards for the mother, real and potential. Post-partum hemorrhage contributes appreciably to maternal mortality. Even more important than the immediate blood loss is the increased hazard of infection introduced by the manipulations necessary to control the bleeding and fostered by the decreased effectiveness of the defensive mechanism as a result of the blood loss. Much of the morbidity or mortality directly attributable to the third stage of labor is never credited to this period.

It is almost a century since Credé studied the mechanism of placental separation and expulsion and suggested his method of management to reduce the high incidence of complications. Many modifications of the Credé method have been tried and found wanting during the intervening years. The introduction of oxytocic drugs led to their immediate adoption in the conduct of this period. However, this new measure failed to decrease the hazards of the third stage to any great extent. The vast majority of clinical teachers prefer not to interfere with this phase of labor, allowing the normal mechanism to operate. This is sound obstetric teaching.

During the past several decades, a number of new factors have entered into the conduct of labor which have seriously affected the course of the third stage. An ever increasing number of patients are confined in hospitals in which natural delivery is decreasing in frequency. Labor is often terminated in the primipara by the combined use of outlet forceps and episiotomy. These advantages necessitate the use of anesthesia. The pain of labor is relieved by various analgesic agents, which are sometimes carried to great extremes in order to eliminate the last shreds of discomfort inherent in physiologic parturition. Analgesia, anesthesia, and the increased incidence of operative procedures all combine to interfere with the normalcy of the third stage, thereby increasing the incidence of complications in this period. It becomes apparent that the

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normal mechanism of the third stage may no longer function safely in many cases, so that it may be necessary to resort to new measures in an attempt to safeguard this critical period in the same way that the other phases of the labor have been safeguarded.

Natural as well as artificial forces may produce an abnormal mechanism in the third stage. Long and difficult labor may reduce the effectiveness of the uterine contractions thereby interfering with a rapid and complete placental separation. The overdilatation of the uterine cavity as a result of a large baby, the occurrence of multiple births, or an excessive amount of amniotic fluid may decrease the uterine muscle irritability and contractility and thereby affect normal uterine action. Inherent defects in the innervation or character of the uterus, about which we are only vaguely cognizant, may lead to an abnormal third stage mechanism. These are examples of failures in the normal physiology of reproduction which must be corrected if we are to prevent serious accidents.

The normal mechanism of the placental stage consists of two distinct phases, separation and expulsion. One cannot and should not initiate the latter until the former is completed. The first phase involves a slow, progressive separation of the placenta from the uterine wall and is brought about by physical changes that take place on the evacuation of the uterine cavity by the fetus.

The placenta normally remains attached to the uterus until the expulsion of the fetus. The sudden diminution in size of the uterine cavity results in a reduction of the surface area of the uterine wall to which the placenta is attached. The semi-rigid, noncontractile placenta cannot alter its surface area, and thus it partially or completely separates from its attachment. The speed with which the reduction of uterine surface area is accomplished determines the completeness of the separation. The initial reduction in the area of the placental site rarely results in complete separation for this process is far too slow and too ineffective. Bleeding occurs at this time behind the placenta but it is doubtful if the accumulated blood clot aids the separation by acting as a wedge. The retroplacental clot is not necessary in the mechanism of separation. In most instances it accumulates as a result of an incomplete separation or after the placenta is separated off the placental site while its expression from the lower uterine segment and vagina has been delayed. Uterine contractions now recur which shear the remainder of the placenta from its attachment. How effective a placental separation is depends on uterine contractility. Many variations in the character of the separation can and do occur. Generally, the longer the third stage lasts, the less complete the placental separation is and the greater the blood loss may be during this period.

It has been recognized from clinical experience that any interference with placental separation is likely to result in an abnormal third stage.

Premature attempts to induce separation by inciting uterine contractility by manipulation of the uterus may well result in an incomplete separation and excessive bleeding. Such uterine stimulation often provokes arrhythmic contractions or localized uterine irritability which interferes with normal placental separation. Premature attempts at expulsion often lead to an increased venous engorgement of the uterus or to the incarceration of an incompletely separated placenta within the contractile zone. To retain the normalcy of the third stage, it is most important not to interfere with the separation phase and to recognize when this phase is complete so that the expulsion of the placenta may be aided.

The use of an oxytocic drug in the third stage of labor was introduced as a means of facilitating the phase of separation in the third stage mechanism, thereby decreasing the hazards of this period. Pituitary extract has been used routinely for many years at the end of the second stage at the Chicago Lying-in Hospital. Its parenteral administration, however, rarely affected the phase of placental separation, for this route of drug administration results in a delay of six or seven minutes in the effectiveness of the drug. Usually separation is completed by natural forces in this period, and the effect of the oxytocic drug is to stimulate the uterus to expel the separated placenta into the distended lower uterine segment and vagina from which it may easily be expressed. Rarely, the oxytocic action occurs before the expulsion of the placenta from the contractile upper segment of the uterus or before separation is complete, in which event the placenta may be incarcerated firmly in this contractile zone. Such an undesirable complication may result in excessive bleeding and complicate placental removal in the event that it is indicated. This hazard decreases the value of this mode of therapy for the third stage.

Since the advent of ergonovine in 1935, further uses for this powerful oxytocic drug have been under investigation. Extensive pharmacologic and physiologic studies have amply demonstrated its profound oxytocic character, its prolonged effect, and the absence of undesirable reactions regardless of the mode of administration. Our early studies indicated that the oral and intramuscular routes were slow in their action, six or eight minutes elapsing from the time the drug was administered to the onset of activity. Intravenously administered, the drug exhibits activity within twenty or thirty seconds. The character of the response varies to some degree with the mode of administration (Fig. 1). When ergonovine is administered orally or subcutaneously, the initial uterine contractions are of moderate intensity and slowly increase in severity over a period of five or six minutes until they reach their maximum intensity. At the same time, there is a progressive increase in uterine tone which reaches its maximum state at the time of the greatest uterine action. This characteristic response to ergot preparations has made the

administered intramuscularly after the baby is born prepares the way for a more favorable phase of expulsion.

In the expression of the placenta, several safeguards must be exercised. The corpus uteri must be in a contracted state before expression begins.

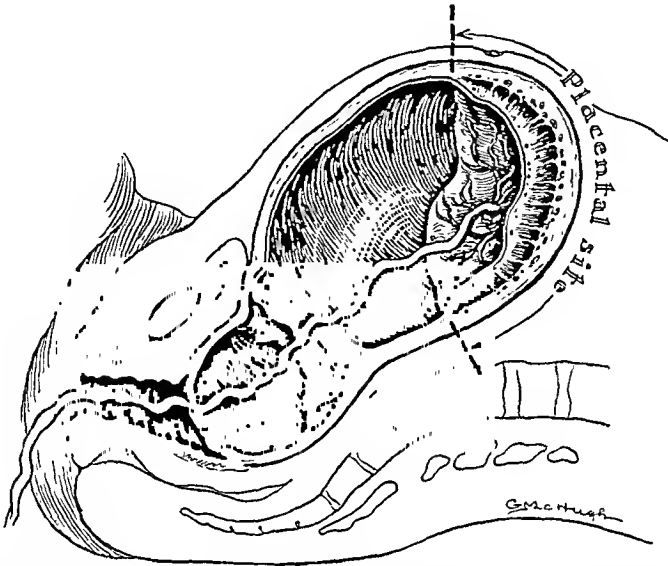


Fig. 2.—Showing the normal uteroplacental relationships when the cavity of the uterus is distended with the fetus. Note the length of the placental site indicative of its surface area and the characteristic discoid shape to the uterus.

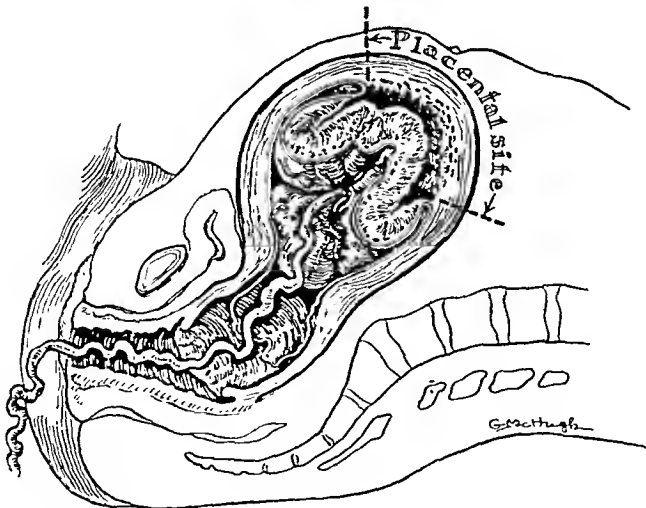


Fig. 3.—Showing the uteroplacental relationships immediately after the baby has been expelled from the uterus and the placenta has separated from its uterine attachment. Note the great decrease in surface area of the placental site, the thickened uterine wall and the change in uterine contours.

The entire uterus must not be pushed downward into the pelvis because this dislodgement leads to excessive bleeding. The venous return is shut off and the uterine sinuses become distended with blood, thereby tending

to increase the blood loss. Pastore has suggested a method to prevent this undesirable complication, but his method is not applicable when the attendant is conducting the labor without help. The left hand is placed flat on the abdomen with the fingers directed under the symphysis, thereby preventing the uterus from entering the pelvis while the right hand expresses the placenta. The same end can be accomplished by the accoucheur if he will make pressure with the fingers of the left hand just above the symphysis while the right hand pushes down on the corpus uteri. When the placenta is visible at the introitus, slight traction on the cord will deliver it most easily. However, traction on the cord is to be seriously condemned under any other conditions, for such manipulation on an incarcerated or partially adherent placenta may result in inversion of the uterus.



Fig. 4.—Showing the uteroplacental relationships after the expulsion of the placenta into the lower segment and vagina. The fundus of the uterus has become globular and has risen; the lower segment is distended by separated placenta.

The advantages of the method described lie chiefly in the marked reduction in the loss of blood and the freedom from complications of the third stage with their associated post-partum hemorrhage. The method has proved so effective on our service that the incidence of serious post-partum bleeding has been greatly reduced. The regime described is applicable only to institutional practice, for it requires someone to give the drug intravenously at the proper moment. Exact timing in the administration of intravenous ergonovine is most essential. There have occurred a few instances of incarceration of the placenta in the contracted zone, but this complication is not troublesome in an institution. The conduct of the third stage described should have particular appeal where patients are predisposed to abnormal uterine bleeding because of a previous post-partum hemorrhage, an excessively distended uterus, a long labor, or difficult operative interventions.

Since Jan. 1, 1938, it has been possible to make careful observations of the third stage of labor in 2,006 patients who had received ergonovine. The duration of the third stage, the blood loss and unusual complications were carefully recorded in each instance. Other factors in the labor and delivery which could influence the third stage were carefully analyzed. The uterine blood loss was measured after careful collection in a basin during and after delivery of the placenta. Bleeding from the episiotomy or perineal lacerations was excluded so far as possible. Since some of the blood from these sources inevitably went into the basin, the figures probably represent a higher loss than actually occurred from the uterus. This error is constant for the several groups of patients studied so that the results are comparable.

The most important part of this study concerns itself with the intravenous use of ergonovine after the head has been delivered and when the easy egress of the shoulders from the birth canal is assured. Two other groups of patients are presented. In both instances, placental separation and expulsion were accomplished by natural forces, following which ergonovine was administered intravenously to the first group and intramuscularly to the second group. All three of these groups are not quite comparable, for ergonovine was used in the second stage whenever there was an increased likelihood of an abnormal placental stage. Furthermore, ergonovine was administered intravenously in all patients in whom the placental stage was prolonged, abnormal, or complicated by an excessive blood loss. The third group of patients who received the drug intramuscularly, represented the patients who had the most normal natural third stage and the drug was given primarily to assure good uterine tone, thereby preventing excessive blood loss.

Table I presents a summary of the three groups of patients in whom ergonovine was used. More than half of the entire group, 1,020 patients, or 50.8 per cent of the total, received the drug during the second stage of labor as described previously. Of this group, 81 per cent of the patients had a measured blood loss of less than 100 c.c. and only 19 per cent lost more than 100 c.c. There were only 4 patients in whom the blood loss was more than 500 c.c., an incidence of less than one-half of 1 per cent. In the group of patients where ergonovine was administered intravenously after the placenta had been expelled from the uterus, 35 per cent lost not more than 100 c.c. of blood, whereas 65 per cent lost more than 100 c.c. It is worthy of note that although this represented a smaller group of patients, 753, there were 15 patients who had a blood loss of over 500 c.c., an incidence of 2 per cent. In the third group of patients in whom ergonovine was administered intramuscularly at the end of the third stage, 46 per cent lost not more than 100 c.c. of blood. There were 5 patients in whom the measured blood loss was more than 500 c.c., an incidence of 4.6 per cent. The striking fact in this résumé is the small blood loss during the third stage of labor in those patients who received ergonovine intravenously in the second stage of labor with the delivery of the shoulders of the baby. There is no comparison

TABLE I. BLOOD LOSS OF THIRD STAGE

	25 c.c.	50 c.c.	100 c.c.	200 c.c.	300 c.c.	500 c.c.	OVER 500 c.c.
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Ergonovine Intravenously in Second Stage

(1,020 cases or 50.8% of total)

Primiparas	41	170	239	101	12	7	2
Multiparas	84	136	158	56	8	4	2
Total	125	306	397	157	20	11	4
Per cent	12	30	39	15	2	1	0.3

81 per cent of these patients lost not more than 100 c.c. of blood (measured), 19 per cent lost more than 100 c.c., and 4 per cent lost more than 200 c.c.

Ergonovine Intravenously in Third Stage

(753 cases or 37.5% of total)

Primiparas	6	14	59	129	55	36	5
Multiparas	17	52	117	152	63	38	10
Total	23	66	176	281	118	74	15
Per cent	3	9	23	37	16	10	2

35 per cent of these patients lost not more than 100 c.c. of blood (measured), 65 per cent lost more than 100 c.c., and 28 per cent lost more than 200 c.c.

Ergonovine Intramuscularly in Third Stage

(233 cases or 11.7% of total)

Primiparas	3	5	18	24	7	9	1
Multiparas	6	26	48	49	20	13	4
Total	9	31	66	73	27	22	5
Per cent	4	13	29	31	12	9	2

46 per cent of these patients lost not more than 100 c.c. of blood (measured), 54 per cent lost more than 100 c.c., and 23 per cent lost more than 200 c.c.

between the third stage in this group of patients and the two groups in whom the use of an oxytocic drug was delayed until after the third stage was complete.

The length of the third stage was much shorter than normal when ergonovine was used at the end of the second stage of labor. Of the total group of 1,020 patients, the third stage was one minute or less in 131, two minutes or less in 369, three minutes or less in 237 (Table II). Thus in 754 cases, or 73 per cent of the entire group, the placenta was delivered in less than three minutes. This confirms the impression that

TABLE II. LENGTH OF THE THIRD STAGE AND BLOOD LOSS

MINUTES	TOTAL CASES	% OF TOTAL	UNDER 200 C.C.	UNDER 50 C.C.	50 TO 99 C.C.	100 TO 199 C.C.	200 TO 299 C.C.	300 TO 499 C.C.	500 C.C.+
<i>Ergonovine Intravenously in the Second Stage—1020 Patients</i>									
3 or less	754	73	98%	335 45%	310 41%	92 12%	8 1%	7 1%	2 0.3%
4-10	237	23	94%	79 37%	84 35%	51 22%	10 4%	2 1%	1 %
11-30	22	2	77%	5 23%	2 9%	10 45%	2 9%	2 9%	1 5%
Over 30	7	1	100%	2 28%	1 14%	4 57%	0 0%	0 0%	0 0%

the separation of the placenta is almost instantaneous, occurring immediately after the passage of the fetus from the uterine cavity, and promoted by the oxytocic effect of the intravenous ergonovine.

There was a direct relationship between the blood loss and the length of the third stage. Thus, 98 per cent of the patients in whom the third stage lasted three minutes or less lost less than 200 c.c. of blood. In many instances the blood loss was infinitesimal in amount as can be noted in Table I. In only 7 patients was the duration of the placental stage longer than thirty minutes, and it is interesting to note that in all of these instances the blood loss was less than 200 c.c. A delayed third stage of labor, following the intravenous administration of ergonovine at the end of the second stage, is not necessarily associated with an increased blood loss.

TABLE III. LENGTH OF THE THIRD STAGE AND BLOOD LOSS

MINUTES	TOTAL CASES	% OF TOTAL	UNDER 200 C.C.	UNDER 50 C.C.	50 TO 99 C.C.	100 TO 199 C.C.	200 TO 299 C.C.	300 TO 499 C.C.	500 C.C.+
<i>Ergonovine Intravenously in the Third Stage—753 Patients</i>									
3 or less	202	27	78%	26 13%	49 24%	84 42%	22 11%	20 10%	1 0.5%
4-10	439	59	72%	52 12%	102 23%	167 37%	76 17%	35 8%	7 2%
11-30	93	13	62%	10 11%	20 22%	27 29%	18 19%	13 14%	5 5%
Over 30	11	0.1	27%	0 0%	0 0%	3 27%	2 18%	4 36%	2 18%
<i>Ergonovine Intramuscularly in the Third Stage—233 Patients</i>									
3 or less	37	15	89%	11 30%	13 35%	9 24%	3 8%	0 0%	1 3%
4-10	155	66	78%	23 15%	45 29%	52 34%	17 11%	15 10%	3 2%
11-30	40	17	66%	6 16%	8 20%	12 30%	7 18%	6 15%	1 3%
Over 30	1	0.4	0%	0 0%	0 0%	0 0%	0 0%	1 100%	0 0%

Table III presents an analysis of the group of patients who received ergonovine intravenously at the end of the placental stage. The effect of the oxytocic drug is demonstrated by the low incidence of post-partum hemorrhage. In more than one-half of the patients in this group, the placental stage lasted longer than four minutes. There was a greater average blood loss than in the preceding group.

Table III likewise presents a summary of the patients who received ergonovine intramuscularly at the end of the placental stage. In the majority of these patients, the length of the placental stage exceeded four minutes. The incidence of post-partum hemorrhage is not great in this group because of the fact that the drug was used intramuscularly only in the patients who had a normal third stage. Where the third stage was abnormal and a tendency to bleeding existed, the drug was administered intravenously. One can conclude that the length of the third stage determines to some extent the blood loss during this period.

Table IV is a summary of the labors in the group of patients who received ergonovine. It will be noted that 163 patients had a natural

TABLE IV. DELIVERY AND BLOOD LOSS

	TOTAL CASES	UNDER 200 C.C.	UNDER 50 C.C.	50 TO 99 C.C.	100 TO 199 C.C.	200 TO 299 C.C.	300 TO 499 C.C.	500 C.C.+
<i>Intravenous Second Stage</i>								
Natural	163	100%	90	61	12	0	0	0
Natural with episiotomy	307	97%	130	121	46	6	2	2
Low forceps	469	96%	183	183	84	13	5	1
Midforceps	64	91%	24	27	7	1	4	1
Breech	8	100%	2	4	2	0	0	0
Dührssen's	15	93%	1	10	3	0	1	0
<i>Intravenous Third Stage</i>								
Natural	271	83%	55	84	83	26	18	5
Natural with episiotomy	304	71%	19	69	130	50	27	9
Low forceps	96	59%	9	8	40	24	15	0
Midforceps	9	0%	0	0	0	2	7	0
Breech	62	73%	6	15	24	12	5	0
Dührssen's	1	0%	0	0	0	1	0	0
<i>Intramuscular Third Stage</i>								
Natural	86	83%	23	28	20	8	6	1
Natural with episiotomy	114	79%	12	32	46	13	11	0
Low forceps	26	51%	3	6	4	5	4	4
Midforceps	0	0%	0	0	0	0	0	0
Breech	7	72%	2	0	3	1	1	0
Dührssen's	0	0%	0	0	0	0	0	0

delivery unassisted in any way. This represents the most normal group of patients who received ergonovine intravenously just before the shoulders were delivered. In all instances the blood loss was less than 200 c.c. and in 93 per cent of this entire group less than 100 c.c. This group provides additional evidence of the diminished blood loss which follows this conduct of the placental stage. The type of delivery does not appear to have any great effect on the blood loss during the third stage of labor.

The intravenous administration of this drug at the end of the second stage was not successfully carried out in breech delivery. It is probably unwise to administer the drug before the baby is completely delivered. Should a premature contraction occur while the aftercoming head is still within the pelvis, great difficulty might be encountered in its delivery. For this reason, it is suggested that in breech delivery ergonovine be given intravenously after the birth of the baby and after the completion of the delivery of the placenta.

Of 16 patients who were delivered after Dührssen's incisions on the cervix, 15 received ergonovine with the delivery of the shoulders. It is of interest that in 14 of these the blood loss was less than 200 c.c. and in only one instance was the blood loss 500 c.c. Anyone who has had experience with this operation, which is usually combined with a difficult forceps, will realize that this result is in marked contrast to the usual experience. Prior to the use of ergonovine, it was necessary to resort to uterine tamponade in about one-third of the patients in whom

Dührssen's incisions were performed because of the prolonged and troublesome bleeding from the uterine cavity.

Table IV likewise presents a résumé of the type of delivery in the patients who received ergonovine intravenously or intramuscularly after the placenta was delivered. The blood loss was appreciably greater in both of these groups than in the former group, and the incidence of post-partum hemorrhage was increased. The type of delivery affected the blood loss only moderately.

Table V presents an analysis of the length of labor in relation to the blood loss during the third stage of labor. It is interesting to note that in 231 patients with short labors who received ergonovine with the delivery of the shoulders the blood loss was less than 200 c.c. in all instances. This is another striking example of the value of ergonovine administered at the end of the second stage of labor. In the group of patients in whom the labor was of average length, the blood loss was less than 200 c.c. in 95 per cent of the patients, whereas in 142 patients in whom the labor was long, the blood loss in 97 per cent was less than 200 c.c. The length of labor did not increase the blood loss nor the incidence of a pathologic third stage in this group.

TABLE V. LENGTH OF LABOR AND BLOOD LOSS*

	TOTAL CASES	UNDER 200 C.C.	UNDER 50 C.C.	50 TO 99 C.C.	100 TO 199 C.C.	200 TO 299 C.C.	300 TO 499 C.C.	500 C.C.+
<i>Intravenous Second Stage</i>								
Short	231	100%	99	99	33	0	0	0
Average	640	95%	283	232	97	18	7	3
Long	149	97%	49	66	27	2	4	1
<i>Intravenous Third Stage</i>								
Short	176	74%	22	39	69	21	20	5
Average	517	72%	60	120	193	85	50	9
Long	60	71%	7	17	19	12	4	1
<i>Intramuscular Third Stage</i>								
Short	62	75%	8	22	17	6	7	2
Average	160	79%	32	42	53	18	12	3
Long	11	46%	0	2	3	3	3	0

*Short labor: Primipara, less than 8 hr. Multipara, less than 4 hr.

Average Labor: Primipara, less than 24 hour. Multipara, less than 18 hr.

Long labor: Primipara, more than 24 hr. Multipara, more than 18 hr.

Table V likewise presents a résumé of the length of labor as it affected the third stage when ergonovine was administered intravenously and intramuscularly after the placenta had been delivered.

TABLE VI. MANUAL REMOVAL OF THE PLACENTA
(25 instances in 2,006 patients)

ERGONOVINE ADMINISTERED	NO. OF CASES	MANUAL REMOVAL	INCIDENCE	BLOOD LOSS (AVERAGE)
Intravenously second stage	1020	8	1:127	200 c.c.
Intravenously third stage	753	15	1:50	393 c.c.
Intramuscularly third stage	233	2	1:116	400 c.c.

Table VI presents the incidence of manual removal of the placenta in the entire group. It will be noted that the incidence of manual removal was once in 127 cases when ergonovine was administered intravenously at the end of the second stage; whereas the incidence increased appreciably in patients in whom the placental stage was left to natural forces and ergonovine was administered on its completion. The fact that the incidence of manual removal was once in 50 in the group which had received intravenous ergonovine at the end of the third stage can be explained on the basis that this procedure was carried out to reduce the hazard of post-partum hemorrhage. Furthermore, it will be noted that the blood loss was half as great where manual removal was necessitated following the use of ergonovine intravenously at the end of the second stage. Careful timing is important in the administration of ergonovine so that its effect can be exerted while the baby's body is still distending the uterine cavity. This procedure allows the baby to pass out of the upper segment, following which a powerful uterine contraction will shear off the placenta promptly. This is the most important factor in the prevention of incarceration of a completely or an incompletely separated placenta. The same uterine force properly timed will likewise expel the placenta from the uterus into the dilated uterine segment and vagina. Its prompt expulsion from this locality should follow.

DISCUSSION

The use of ergonovine intravenously as the baby emerges from the birth canal involves no new mechanism for placental separation and expulsion, but it perfects the normal mechanism. The powerful oxytocic drug administered when the baby is still distending the uterine cavity assures uterine contraction of maximum intensity as the baby leaves the birth canal. Such complete uterine action produces ideal physical conditions for prompt and complete placental separation. As the placental site suddenly shrinks away from the non-contractile placenta, the latter is cleanly sheared off its attachment. The same uterine contraction pushes the completely separated placenta from the contractile zone into the distended lower uterine segment and vagina. The marked uterine tonicity which is induced by ergonovine guards against further blood loss following placental separation. The drug likewise will maintain a state of tonicity for several hours, thereby preventing delayed post-partum bleeding.

The success of this third stage mechanism depends to a great degree on an accurate timing of the several events which comprise this period. Poor timing may result in the separation of the placenta, but it may be trapped in the contracted portion of the uterus. More rarely, a partially separated placenta may be incarcerated within the uterus. These accidents need not result in an excessive blood loss. After a short time the uterus may relax and the placenta can be easily expressed. In rare instances, manual removal of the placenta may be indicated. In spite of the fact that the drug has been in use during the past three and a half years by a host of physicians in training, these accidents occurred very

infrequently. The freedom from serious hemorrhage and complications in the third stage has been the most striking observation in this entire study. During the past two years the conduct of the third stage of labor just described has become routine on the House Service at the Chicago Lying-in Hospital.

CONCLUSIONS

A new method of conducting the placental stage of labor is described. Ergonovine is administered intravenously after the fetal head has been delivered and when easy egress of the shoulders has been assured. This results in an instantaneous separation of the placenta and its expulsion into the distended lower uterine segment and vagina. This procedure is applicable only to hospital practice. The marked reduction in blood loss and the very low incidence of complications in the third stage should result in a marked decrease in post-partum hemorrhage and its undesirable sequelae. Detailed observations are recorded in 2,006 patients, more than one-half of whom were treated by this new procedure.

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DISCUSSION

DR. W. C. DANFORTH.—Ergonovine is a valuable addition to our list of obstetric resources. I have had no experience with it in the third stage of labor, but we have for a long time used it routinely by intramuscular administration immediately after the delivery of the placenta. Blood loss has been diminished and uterovaginal tamponade for bleeding has become notably less in frequency.

The saving of blood at the time of delivery is important. Few clinics are accurately aware of the amount of blood which is lost for, without some form of measuring device, exact knowledge is impossible. It is certain that many estimates are inaccurate.

The mechanism of placental separation is better understood today than it used to be. The action of the contracting uterine muscle in severing the attachment of the noncontractile placenta is well brought out in the paper. Interference with this mechanism by early massage is properly criticized. Too early attempts to express the placenta often disturb the progress of separation and hinder rather than help.

If the process of separation and expulsion can be shortened without disturbing normal mechanism it is worth while. If normal mechanism is altered one cannot approve. In some of the radical suggestions for terminating the second stage or for initiating labor the normal series of events is changed. This must invite morbidity if not mortality.

The careful observations of the essayists seem to show that, although the process of delivering the placenta is hastened, the mechanism is not changed. That separation of the placenta must be complete before any attempt at expulsion is made is an obstetric law, the validity of which is recognized by the essayist.

That the use of an oxytocic in the third stage will reduce the time required for separation seems to be shown by our own experience with pituitrin, for the length of the third stage has decreased from fifteen to twenty minutes to about seven. The time, however, is a matter of secondary interest. The amount of blood loss is far more important. The tables indicate that the amount of blood lost has been materially decreased. If 81 per cent of more than 1,000 patients lost not more than 100 c.c. and only 4 per cent lost more than 200 c.c., the suggestion of the essayists commends itself seriously to us.

The old teaching, that ergot should never be given to an undelivered woman, with the single exception of abruptio placentae, was good. The prohibition of interference with the placental stage was also sound. Nonetheless, with the very greatly increased efficiency of the new alkaloidal preparation a change may be permitted. All forms of management should give way when demonstrably better ones appear.

DR. ROBERT M. GRIER.—In the past year at the Evanston Hospital, we delivered 1,004 mothers. Only 12 of these women had sufficient bleeding to warrant calling the condition a post-partum hemorrhage. Thirteen women had their uteri packed. Formerly hemorrhage was copious enough to require packing of the uterus about 35 times a year. Since we have been using ergonovine intravenously where serious bleeding appeared, this number has been reduced to one-third.

The response to ergonovine given intravenously can be felt within thirty seconds while one holds the uterus. We do not, however, inject ergonovine routinely at the end of the second stage as has been recommended by the essayist. We have employed it intravenously at the end of the third stage only when it was felt necessary, but give it intramuscularly routinely at that time.

DR. LOUIS RUDOLPH.—The essayists have indicated four cases in which the blood loss was 400 c.c. or more. I would like to inquire, why do we sometimes get hemorrhage in spite of the use of ergonovine? It is well known also that a severe post-partum hemorrhage may occur with a flaccid or fairly well-contracted uterus in which hysterectomy is necessary to save life.

Duncan and others have indicated that the maternal sinuses of the placental site are first closed by the contraction phase of the muscle tissue of the placental site. The contracted state of the maternal sinuses of the placental site is maintained by the specific property of brachystasis of the upper uterine segment of the parturient uterus. Dr. Davis has clearly shown that the uterine response to ergonovine is due to the property of muscle contractility, but it does not imply that brachystasis (retraction) has taken place.

The combined properties of contraction and brachystasis (retraction) lead to decreased and tortuous lumina of the maternal sinuses, stasis, and thrombosis, and these when maintained lead to organization. On the other hand, if the uterus responds only to the contraction phase, relaxation will follow and hemorrhage will occur from the maternal sinuses, on account of the absence of the essential property of brachystasis.

We do not know what controls brachystasis, but it is a specific property of the upper uterine segment of the parturient uterus. All oxytocics will cause increased contractility, but we do not know that they play any part in bringing about brachystasis. Ergonovine increases contractility, and with a normal degree of brachystasis of the uterine musculature it decreases the hemorrhage from the maternal sinuses. It is, however, no guarantee against post-partum hemorrhage.

DR. FRED L. ADAIR.—I would like to call attention to a point in the normal mechanism of separation of the placenta which is not exactly in accordance with what takes place when any stimulation of the uterus occurs following the adminis-

tration of ergonovine. When the uterus contracts after delivery, the portion of the uterine wall which is not covered with placenta becomes somewhat thickened while the uterine wall which underlies the placenta does not. As the normal process proceeds a gradual separation of the placenta occurs, as this portion of the uterine muscular wall contracts, thus completing the first phase of the third stage.

When ergonovine is administered just after the child's head is delivered, the whole uterus contracts, including that portion underlying the placenta, and so the first phase of the third stage is virtually completed before the child is expelled. By the time the child is outside the uterus the separated placenta lies in the uterine cavity. In other words, in the normal mechanism when the child is expelled there is still an uncontracted portion of the uterine wall at the placental site, whereas with the administration of ergonovine the first phase of the third stage is practically completed when the child is delivered.

With the increased number of operative deliveries, it is quite important that the subsequent procedures, such as repair, not be delayed. If you wait fifteen to thirty minutes for the normal expulsion of the placenta, it means that the patient has either to come out of the anesthetic or the anesthesia is continued for a longer period of time, both of which are more or less undesirable. This plan of treatment means that we can proceed more promptly with the post-partum care immediately following delivery of the placenta. Further, we have the very important fact that with a minimal loss of blood we resort less frequently to vaginal and uterine tamponade in order to clear the field for the repair of lacerations or repair of laparotomy wounds. Tamponade carries the danger of the introduction of infection.

DR. JOSEPH L. BAER.—We at Michael Reese Hospital likewise lend our approval to this procedure. However, the use of an oxytocic which is so potent requires more emphasis on the dangers than the essayist gave it. He spoke properly of the accurate timing of administration of this drug, and he mentioned that the shoulders should be impinged under the symphysis. This procedure is now to be published with the approval of a very considerable group, an authoritative group, including those who have discussed this paper. I can imagine the possibility of rupture of the uterus due to the violence of its contraction against the impacted shoulders, the head being completely delivered but the shoulders not having come through the inlet. Hence I think when this article goes into print there should be very decided emphasis placed on the specific risks that are inherent in this procedure. There is a place for this oxytocic if it is used according to the directions given and with foreknowledge of the potential dangers.

Finally, I would like to have Dr. Davis tell us their method of measurement of blood loss, because these measurements were given rather accurately in 100 c.c. units.

DR. DAVIS (closing).—We hesitated for a period of about three years before presenting this new management of the placental stage to the profession. In the interim, our method has been carefully investigated and approved in several other institutions. It was our impression, as Dr. Baer so well brought out, that if doctors found they could deliver the placenta in a fraction of a minute, or within a minute or two, that they would resort to the use of intravenous ergonovine indiscriminately. We felt that widespread use of this procedure could possibly result in serious consequences. We are convinced that the discriminate and intelligent use of the procedure described is safe.

I was interested in Dr. Grier's comment concerning uterine tamponade. I should like to tell you our experience in this regard. Prior to 1938 at the Chicago Lying-in Hospital we packed the uterus of about three women each month. In going over our statistics I found that uterine tamponade was carried out in 1 per cent of our deliveries, or 30 to 35 patients a year. During the last two years we resorted

to this procedure in a total of three instances. In two of these patients the tamponade was necessitated because of trauma. In all instances where intravenous ergonovine fails and the patient continues to bleed, a careful investigation of the reproductive tract should be made to rule out trauma as a cause of the bleeding. We have reduced the incidence of complications of the third stage tremendously since we have instituted the plan which we described.

One other thing I should like to point out is the use of ergonovine in breech delivery. We have been interested for many years in the use of an oxytocic drug in such cases. However, by the time the aftercoming head has left the uterine cavity and has reached the level of the perineum, the favorable mechanism for ergonovine intravenously has been lost. The drug should exert its influence when the uterine cavity is still distended with the baby's body. Obviously, in breech delivery this is not sound. In breech delivery ergonovine should not be administered intravenously until the placenta has been delivered. It can be given safely intramuscularly immediately after the baby is delivered so that its action will be delayed until placental separation and expulsion from the upper segment has been accomplished.

The method of estimating blood loss provides for considerable error. All the blood escaping from the vagina from the time the infant was delivered until the placenta was expressed was carefully collected by placing a basin at the buttocks. This basin was removed when there was no more bleeding from the uterine cavity and vagina. Obviously, some blood from the episiotomy was included in the measured loss. Our figures, therefore, represent more than the loss associated with placental separation and its delivery. Many women lose so little blood that the amount is difficult to measure, providing a bloodless placental stage.

Cobb, D. B.: Posterior Vaginal Hernia, *South. M. J.* 34: 196, 1941.

A ten-year review of the literature revealed only 42 reports dealing with this condition, and to these the author adds three of his own. The anatomic basis for posterior vaginal hernia is the weakness of the pelvic sling at the bottom of the pouch of Douglas where there is very little muscle tissue and scant fascial support. Excessive depth of the cul-de-sac may be a predisposing factor. The sac, which develops as elongation from the bottom of the pouch of Douglas, dissects between the layers of the rectovaginal septum and bulges beneath the posterior vaginal wall to emerge in the perineum; thus, it is a variety of perineal hernia. There may or may not be an associated general relaxation of pelvic structures.

There are no symptoms that are characteristically associated with this condition. The diagnosis, though easy to establish, is frequently missed because the lesion is not considered as a diagnostic possibility, and it is confused with the more common simple rectocele. Both may, however, co-exist. The hernia appears when the patient strains, and recedes when the recumbent position is assumed. When the examining finger in the rectum is pressed forward, the bulge of the posterior vaginal wall does not account for the entire vaginal mass, and the hernial sac can be seen and felt. Of significance is "the return of posterior vaginal protrusion after one or more operations for the relief of supposed rectocele."

The principles underlying cure of the condition are isolation and obliteration of the sac with repair of the defect. The condition of the pelvic floor and the presence of any associated genital abnormalities will influence the choice of procedure. Operation may be vaginal, abdominal, or combined abdominoperineal.

ARNOLD GOLDBERGER.

CLINICAL AND PHYSIOLOGIC ASPECTS OF UTERINE MOTILITY DURING PREGNANCY AND LABOR*

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THE analysis of uterine motility, here presented, is based upon the clinical study and recorded surface displacements secured with the capaciograph and mechanical ink writing recorder described in previous articles in this JOURNAL.^{1, 2} The use of equipment which can be used in a routine manner in the study of the motor activity of the uterus has one great advantage; namely, the accumulation of sufficient data to allow for statistical analysis. Thus, the collection of data becomes of minor importance; whereas, the analysis of the massed data becomes of major importance. Five hundred and two patients were studied and represent routine sampling of hospital admissions over a period of twelve months, during which about 3,000 patients were admitted. Over 5,000 large and over 5,000 small tracings of uterine contractions were available for analysis.

In this series there were 248 primiparas and 254 multiparas. Thirty cases were excluded from the series in the present study (19 multiparas and 11 primiparas) due to the employment of pituitrin or its derivatives. In view of the subsequent statistical analysis the classification as given in Table I is of considerable importance.

From the tabulated data, it is apparent that 89 multiparas and 93 primiparas were without pathology or medication. There are 144 primiparas and 146 multiparas who received medication or had some form of pathology or pathologic labor. One hundred and twenty-four of these received medication. Twenty-seven were mechanically induced while the remainder were distributed as shown in Table I. Furthermore, 47 of the primiparas and 64 of the multiparas were admitted with prematurely ruptured membranes, the majority having no pain on admission. The remainder had early, usual, or delayed rupture of the membranes.

In order to analyze our results statistically and to present a guide for future investigations, based upon the use of equipment measuring uterine displacements, the following classifications and standards were adopted.

*Experimental work done at the Department of Obstetrics and Gynecology, University of Chicago and the Chicago Lying-in Hospital.

TABLE I

	MULTIPARAS	PRIMIPARAS
No pathology, no medication	89	93
Sedation (morphine, scopolamine, phenolbarbital, dilaudid)	15	55
Progesterone	4	5
Castor oil and quinine	38	17
Pre-eclampsia	23	18
Mechanical induction	16	11
Section	19	10
Essential hypertension	14	5
Breech	2	11
Placenta previa	1	1
Abruptio placentae	2	1
Fibroids of uterus	1	3
Rupture of uterus	1	1
Arcuate uterus		1
Toxemia	5	2
Twins	3	
Hyperemesis		2
Renal disease	2	1

Any single contractural response was classified as large, small, or compound. Fig. 1 illustrates what is meant by a large single contraction, Fig. 2 a small single contraction, and Figs. 3 and 4 the compound contractions. The actual displacement of the abdominal wall in centimeters was obtained by dividing the recorded displacement by the amplification factor of the recorder. Measurements of recorded displacements are made from the abscissae to the summits of the curves. The over-all duration in seconds of the curve from beginning to end was ascertained. The onset was measured from the point whence the curves first left the abscissae, and from the end where the curve returned to the abscissae. The duration of the contractural phase (ascent) was measured from the onset to the summit and the relaxation phase (descent) from the summit to the termination of the curve. The over-all duration of the compound contractions was determined as in single curves, while the durations of the contraction and relaxation phases were ascertained by selecting the highest summit present in the curve and using that point as indicative of the end of contraction and onset of relaxation.

Since a complete recording represents a series of recurrent single contractions, the complete recordings were classified as consisting of intermittent large, small, mixed large and small, or compound contractions. Fig. 1 is an example of 3 recurring large contractions, Fig. 2 an example of 5 recurring small contractions, while Figs. 3 and 4 are examples of mixed large and small contractions. Intermittent recurrence of curves shown in Figs. 3 and 4 would be an illustration of sequential compound contractions. The complete recordings were analyzed in terms of frequency of (large, small, large and small, compound) contractions per hour. This was readily accomplished by noting the interval of time consumed by a fixed number of contractions, thence

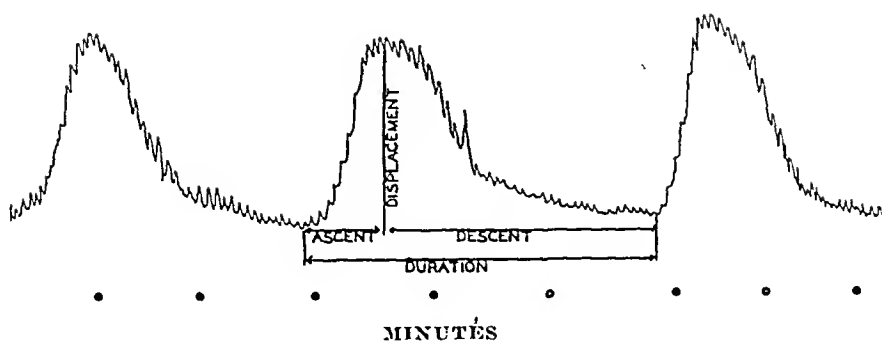


Fig. 1.

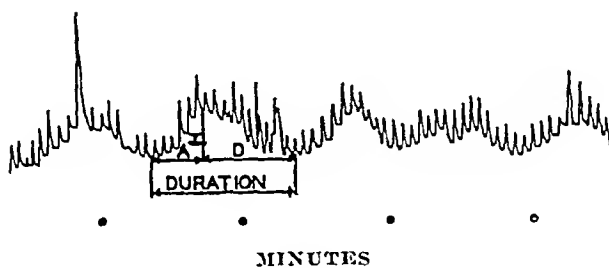


Fig. 2.

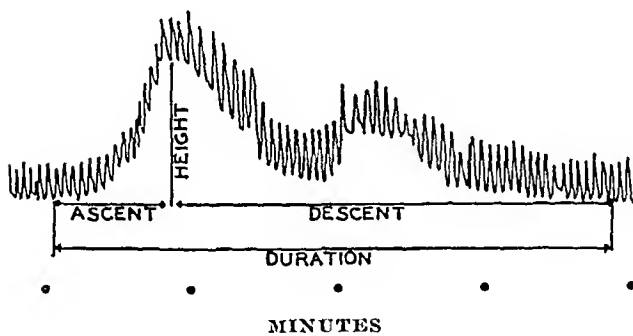


Fig. 3.

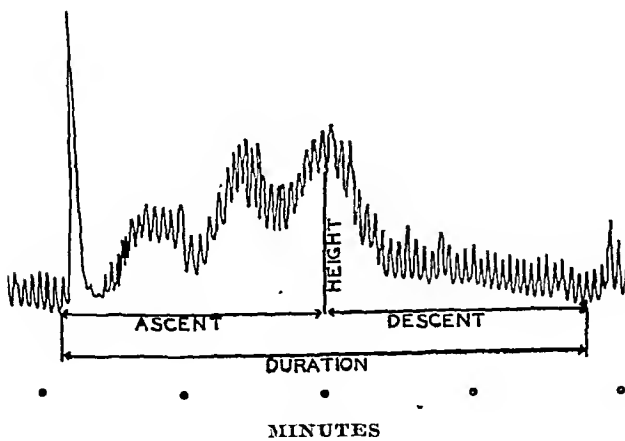


Fig. 4.

by mathematical calculation determine the theoretical number of contractions which would occur per hour.

The actual displacements in centimeters of all large unselected contractions present in all recordings and secured from all the patients studied were subjected to statistical analysis. The following formulas were used throughout in the statistical analysis.

$$\text{Arithmetical Mean } \bar{x} = \frac{\sum (f \times \text{M.P.})}{N}$$

$$\text{Standard Deviation } \sigma = \sqrt{\frac{\sum f (d')^2}{N} - \left(\frac{\sum f d'}{N}\right)^2}$$

$$\text{Standard Error } \sigma_{\bar{x}} = \frac{\sigma}{\sqrt{N}}$$

$$\text{Significance Ratio} = \frac{\bar{x} - \bar{y}}{\sqrt{\left(\sigma_{\bar{x}}\right)^2 + \left(\sigma_{\bar{y}}\right)^2}}$$

Histograms constructed of the tabulated frequency distributions of the collected data show extremes of displacements varying from 0.1 cm. to 3.75 cm. For the most part these extremes represent the range of the recording equipment having an amplification of 4 to 1, rather than the true extremes known to occur from observations in which 0.1 mm. displacements were recognized with an amplification of 40 to 1. On the other hand with a 1 to 1 ratio, displacements of approximately 6.25 cm. have been recorded. From the grouped data, the arithmetical mean for the actual abdominal displacements secured from the combined recordings for multiparas and primiparas was 0.98 cm. The standard deviation was found to be 0.53 cm.

In order to determine possible basic differences in actual displacements in the records secured from unselected multiparas as compared to unselected primiparas, the large displacements of each class were treated separately and in a similar manner. Statistical comparison was then made with a resultant finding of a significance ratio of 2.45. A probability thus exists that the average displacement is larger in multiparas when treated as a class, than in a similar number of unselected primiparas.

The over-all durations of all large contractions were investigated. The arithmetical mean was found to be 154.8 seconds with a standard deviation of 60.28 seconds. Comparing the findings obtained from multiparas with those obtained from primiparas shows that a significant difference exists between the two classes. The average duration of the contractions of multiparas in the series were longer than the contractions of the primiparas.

The contraction phase and relaxation phase durations of the curves were analyzed to ascertain if the previously noted differences persisted.

The arithmetical mean for the contraction phases of all curves was 66.9 seconds with a standard deviation of 31.7 seconds. There exists a probable statistical difference between the primiparas and the multiparas. The contraction phase in multiparas is longer than the same phase in primiparas. The relaxation phase for all curves shows a mean of 88.4 seconds and a standard deviation of 43.6 seconds. The relaxation phase of the curves secured from multiparas tend to be longer in duration than similar phases secured from primiparas.

The arithmetic means and standard deviations found for the combined unselected multiparas and primiparas, unselected multiparas, and unselected primiparas are found in Table II (A, B, G). This table shows that the arithmetical means and standard deviations for displacements, over-all duration of contractions, duration of the contraction phase and relaxation phase are larger for the unselected multiparas than for the unselected primiparas. The respective significance ratios obtained by statistical comparison are shown in Table III (K). The significance ratios indicate that the differences are real and not due to chance.

In order to gain additional insight relative to the factors concerned in producing the observed large standard deviations and ascertain what would perhaps represent the "normal," the analysis was carried out on what is designated as "selected" cases. By a process of exclusion, all cases of sedation, premature rupture of membranes, twins, placenta previa, etc., were eliminated. The recordings used were obtained from those cases listed under "No medication, No pathology" and conforming to the following standards: Duration of pregnancy: 38 to 42 weeks; membranes ruptured at the usual time; duration of clinical labor: primiparas, twenty hours or less, multiparas, fifteen hours or less. Recordings limited to those obtained from primiparas zero to twenty hours before delivery, multiparas zero to fifteen hours before delivery.

The arithmetical means and standard deviations obtained from the recordings secured from "selected" primiparas and "selected" multiparas, gravida ii to xviii were compared with those obtained from unselected primiparas and unselected multiparas. The comparison of unselected primiparas and selected primiparas. Table II (G versus H) shows a definite improvement in the standard deviation for the duration of the contraction phase, relaxation phase, and over-all duration of the contractions. At the same time there was a reduction in the arithmetical means of the respective responses. Inspection of the frequency distribution curves of tabulated data shows greater symmetry than similar curves obtained from the unselected primiparas. The significance ratios obtained by statistical comparison are shown in Table III (G).

The comparison of the unselected multiparas and selected multiparas, gravida ii to xviii (Table II, B versus C) discloses improvement in the

TABLE II. ARITHMETIC MEANS AND STANDARD DEVIATIONS

	CONTRACTION PHASE		RELAXATION PHASE		OVER-ALL DURATION		DISPLACEMENT		FREQUENCY PER HOUR	
	\bar{x}	σ	\bar{x}	σ	\bar{x}	σ	\bar{x}	σ	\bar{x}	σ
(A) Combined unselected multiparas and primiparas	66.38	32.33	88.48	43.64	154.86	60.28	0.98	0.54	17.5	8.96
(B) Unselected multiparas. Gr. ii to xviii	67.80	32.03	91.19	46.90	158.99	63.07	1.03	0.57	16.3	8.70
(C) Selected multiparas. Gr. ii to xviii	69.57	28.42	91.67	50.12	161.24	69.04				
(D) Selected multiparas. Gr. ii to vi	65.45	23.90	86.37	42.39	151.82	51.64				
(E) Unselected multiparas with premature ruptured membranes. Gr. ii to xviii	64.42	28.13	82.24	39.70	146.66	54.81				
(F) Select multiparas with premature ruptured membranes. Gr. ii to vi	64.86	28.16	83.60	40.96	148.46	54.51	0.96	0.50	18.5	8.90
(G) Unselected primiparas	64.96	31.80	86.76	37.90	151.72	55.78				
(H) Selected primiparas	60.09	25.71	80.16	31.31	140.25	47.56				
(I) Unselected primiparas with premature ruptured membranes	68.72	37.58	84.02	41.32	152.74	59.21				
(J) Selected primiparas with premature ruptured membranes	67.29	41.44	84.75	32.83	152.04	46.80				

weight at a rate of only 2.2 per cent daily. Hence, the rabbit is growing about 11 times as rapidly as the goat. Is there a corresponding difference in the rates of supply of Na per unit weight of fetuses? Table II also shows that at this time the rabbit fetus is receiving about 13 times as much Na per unit weight as the fetus of the goat.

A clear concept of this relationship among the relative growth rates of the several kinds of fetuses and their corresponding rates of supply of Na can be obtained from comparing K of Table II from animal to

TABLE II. RELATIONSHIP BETWEEN RATE OF SUPPLY OF SODIUM PER GRAM FETUS (Na_F) AND RELATIVE GROWTH RATE OF FETUS (RGR). THE CONSTANT K IS CALCULATED FROM THE RELATIONSHIP: $K = \frac{\text{RGR}}{\text{Na}_F}$

ANIMAL	GESTATION PERIOD IN TENTHS OF TOTAL											
	0.6-0.7			0.7-0.8			0.8-0.9			0.9-1.0		
	RGR	Na_F	K	RGR	Na_F	K	RGR	Na_F	K	RGR	Na_F	K
Goat	2.9	0.089	33	2.2	0.069	32	2.0	0.055	54	2.0	0.05	40
Cat	15	0.27	64	10	0.17	61	7.5	0.13	57	6.0	0.13	46
Guinea pig	12	0.46	26	10	0.39	25	8.0	0.33	24	8.0	0.28	28
Rat	62	1.0	60	52	0.75	60	47	0.79	60	38	0.63	60
Rabbit				25	0.92	27	19	0.79	24	27	0.93	30
Sow	5.8	0.0079	730	4.4	0.0062	710	3.3	0.0056	580	3.0	0.0050	580

animal. The value of K is of the same magnitude throughout with the unexplained exception of the sow. The maximum variation occurs between the cat and rabbit, the value of K in the cat being about twice that in the rabbit. It consequently becomes possible, knowing the value of K for a single fetus (guinea pig or rat, or rabbit, or goat, or cat), to estimate with a fair degree of accuracy the rate of transfer of sodium to any other fetus (excepting the sow) if the data, which are at hand, on the growth of that fetus are used.

A fundamental question that must be answered before placental physiology is completely understood was mentioned in the introduction. Does the placenta behave like an inert membrane between the maternal and fetal circulations, or does it contribute energy in the transfer of material from mother to fetus, thereby becoming a secretory organ? Before this problem can be solved, it is probable that the transfer rate of many physiologic substances across the placenta will have to be investigated not only from the mother to the fetus, but also in the reverse direction, from the fetus to the mother. The results of the present series of studies do not provide evidence either for or against secretion.

SUMMARY

The transfer of sodium across the placentas of six different animals at progressive stages of the gestation period has been studied. The rate of transfer of sodium per gram of placenta increases in each animal as gestation proceeds until just before term, at which time there is a sharp decrease. The variation in rate of transfer across the placentas has been correlated with morphologic changes in the placenta.

The animals have been chosen to give at least one representative of each of Grosser's morphologic types of placentas. The rates of transfer of sodium across unit weights of these four types of placentas have been found to depend upon the morphologic structure of the placenta: the smaller the number of tissue layers placed between maternal and fetal circulations, the greater the rate of transfer across a unit weight of the placenta.

A correlation was found to exist between the supply of sodium transferred to a unit weight of fetus and the rate at which that unit weight of fetus was growing. This constant observation in all of the animals studied leads us to propose the hypothesis that the underlying principle of placental function is that the rate at which a physiologic substance is transferred to the fetus shall parallel the relative growth rate of the fetus.

We are grateful to the staff of the Department of Terrestrial Magnetism, Carnegie Institution of Washington, for their generous help and advice. We are much indebted to Dr. Dean B. Cowie of the National Cancer Institute and to Dr. B. R. Curtis, Jefferson Physics Laboratory, Harvard University, for preparing the radioactive sodium with the Carnegie generator and the Harvard cyclotron.

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DIFFUSE LUTEINIZATION OF THE OVARIES ASSOCIATED WITH THE MASCULINIZATION SYNDROME

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CONSPICUOUS masculinizing changes in the human female have been associated with a variety of lesions of the endocrine glands. Certain among these appear to be unequivocally responsible for the clinical syndrome; namely, hyperplasia, adenoma or carcinoma of the adrenal cortex, and arrhenoblastoma or adrenal rest tumors of the ovary. The primary importance of other lesions including basophile cell changes in the pituitary (Cushing's syndrome), or thymic neoplasms has been seriously questioned in recent years.¹² It has been shown in a large number of cases of so-called pituitary basophilism in which autopsy reports were available, that either hyperplasia or adenoma of the adrenal cortex was present in addition to the hypophyseal lesion.³ Furthermore, in 2 to 3 per cent of routine post-mortem examinations, small basophilic adenomas of the anterior pituitary gland have been uncovered purely incidentally, without evidence of virilism.¹³ Similarly, in those cases attributed to thymic tumors, adrenal cortical hyperplasia was also found, while the pituitary gland was reported as negative.¹⁷ Thus, in a consideration of the syndrome of masculinization, exclusive of those cases associated with defeminizing tumors of the ovary, it appears that the common, morphologic denominator responsible for the symptom complex may well be either hyperplasia or neoplasia of the adrenal cortex.

In this report we are primarily concerned with the status of the ovaries in such cases. Clinical descriptions of the syndrome indicate that the ovaries are generally small or normal in size, and that evidence of genital regression is usually present, associated with oligomenorrhea or amenorrhea. In this laboratory, we have had the opportunity of studying the post-mortem material of 10 cases of virilism; 7 with cortical adenoma and 3 with carcinoma of the adrenal gland. Of these, all had experienced amenorrhea of three to seventeen months' duration. Examination of the ovaries showed them to be small or normal in size, with little evidence of follicular activity. Recent corpora lutea were not present, corpora albicantia were relatively conspicuous, and the small cystic follicles occasionally encountered were atretic. A survey of the literature in which full autopsies were reported substantiated these findings.^{2-4, 6, 10, 11, 15, 18, 19} The gonads were generally described as small, atrophic, fibrotic, senile, or sclerotic, containing some atretic follicles

and old corpora albicantia. In only one instance, published by Bergstrand in 1934, did the ovarian changes approach those described in this report.¹

It would seem from the above findings that a palpable enlargement of the ovaries is not to be expected in patients manifesting adrenogenitalism. Indeed, in those cases of virilism in which an ovarian enlargement or tumor is found on pelvic examination, the suspicion of a masculinizing ovarian tumor must be entertained. It is the purpose of this report to demonstrate that the latter assumption may be false, for in the two cases described below, a typical clinical picture of masculinization was found associated with enlarged ovaries, due, not to an arrhenoblastoma or adrenal rest tumor, but to diffuse lutein changes particularly involving the theca interna cells.

CASE 1.*—M. G., a 32-year-old negress, was admitted to the City Hospital of New York in 1934. She had been married for two years and had never been gravid. The menses had begun at 13 years, and were always irregular, with amenorrhoeic periods up to four months. The menstrual flow, though at times scanty, occasionally continued for one to four weeks. Obesity had been present since the menarche. Progressive hirsuties of the face and chest continued from the age of 16, necessitating shaving at regular intervals. Metrorrhagia had been present for eight months before admission. On pelvic examination both ovaries were found to be enlarged to about twice normal size. A preliminary dilatation and curettage revealed "a small amount of tissue." A laparotomy was then done and both ovaries removed. The ovaries were uniformly enlarged. On section there were several cystic follicles, while the solid portions of the ovary had a distinct yellowish hue. A portion of the ovaries was made available to us for microscopic study.

Three years later in 1937 the patient was admitted to the Mount Sinai Hospital for further investigation. The obesity and hirsuties were still present (Fig. 1). She was amenorrhoeic and complained of frequent hot flushes. Examination revealed the following: There was diffuse trunk and girdle obesity, while the extremities were relatively normal. The face was round and obese, and the neck short and thick. She weighed 188 pounds and was 5 feet, 3 inches tall. There was a conspicuous hypertrichosis of the face and chest, with a tendency to a male type of esutcheon. The clitoris was not enlarged. Blood pressure was 140/80; urinalysis, negative; basal metabolism, +2 per cent; the blood count showed no abnormalities; blood Wassermann reaction, 1+; sedimentation time, normal. The pupils were unequal. The visual fields were normal. X-ray of the sella turcica revealed no abnormalities. Intravenous pyelogram was negative, without evidence of distortion of the upper calyces of the renal pelves. Perirenal insufflation outlined the right adrenal gland, but showed no abnormalities in its contour. On bimanual examination the uterus was found to be small and the pelvis clear.

Our interest in this patient had been stimulated originally by the unusual ovarian findings. Despite the absence of a demonstrable lesion of the anterior hypophysis or adrenal gland, the clinical picture was

*We are indebted to Dr. Maurice Rashbaum and Dr. James R. Lisa of the City Hospital for the opportunity to study this case.

classified as one of adrenogenitalism, unaffected by previous bilateral oophorectomy. Further follow-up was not obtainable.

Histology of the Ovaries.—The ovarian parenchyma presents a most striking histologic change. Scattered throughout the cortex and medulla are numerous groups of large, foamy cells. These are distributed diffusely throughout the ovary in irregular strands or accumulations of varying size (Fig. 2). They resemble well-developed, luteinized theca cells. They are large, round or oval, with light staining, finely vacuolated cytoplasm, round vesicular nucleus and distinct nucleolus. The picture brings to mind the so-called "interstitial gland" sometimes

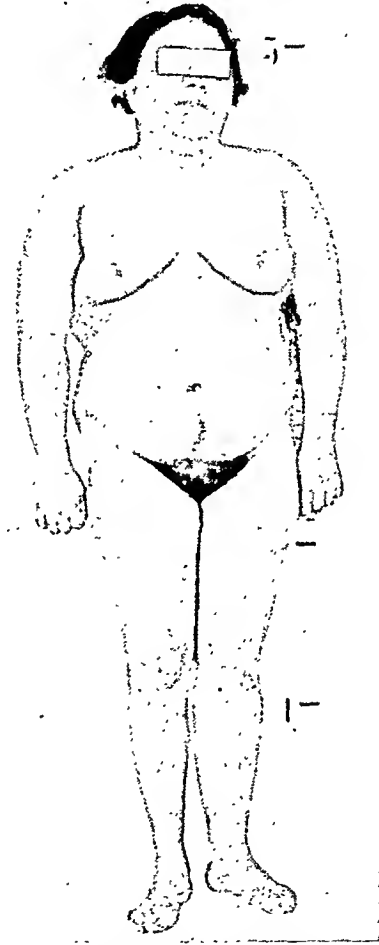


Fig. 1.—Case 1. Masculinizing changes associated with enlarged, luteinized ovaries. Note girdle, trunk, and facial obesity. The patient shaved regularly. Oligomenorrhea and metrorrhagia had been present since the menarche.

seen in ovaries of lower animals, or the diffuse, parenchymal luteinization encountered in mice following x-ray.⁸ The presenece of these cells adjacent to old corpora albicantia suggests at first glance, a possible origin from dormant theca cells about the corpora albicantia. The latter, however, are so numerous that the contiguity may be merely coincidental. Furthermore, the luteinized cells appear elsewhere in areas free of follicle structures. The ovarian parenchyma suggests increased proliferation, not only because of the increased thickness of the ovary, but also because the parenchyma shows distinct variations in cellularity, staining reaction, and size and shape of the cells. The theca zone about

atretic follicles is increased in thickness. Even in atretic follicles where the granulosa is reduced to a single layer of flattened cells, the theca cells show excessive proliferation and luteinization (Fig. 3).

CASE 2.—B. G. (Admission No. 405620, Path. No. 58999), aged 27 years, married five years, gravida 0. Regular menstrual periods had occurred from the menarche at 13 years until the age of 22 years. In

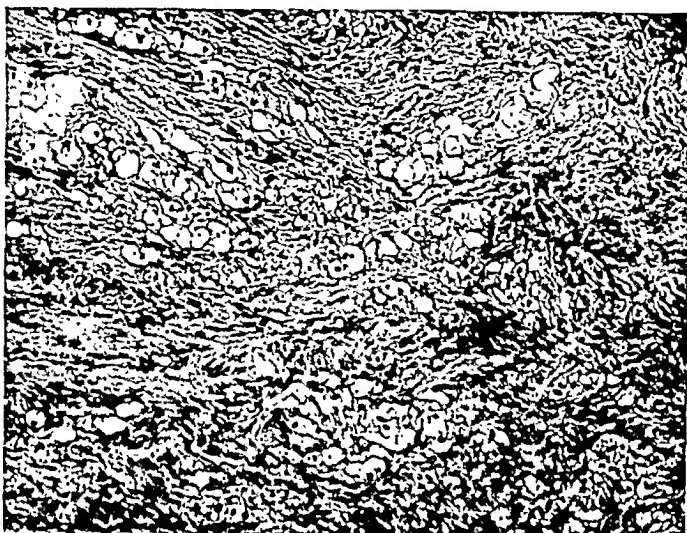


Fig. 2.—Case 1. Groups of enlarged, luteinized cells, irregularly scattered throughout the ovarian parenchyma.

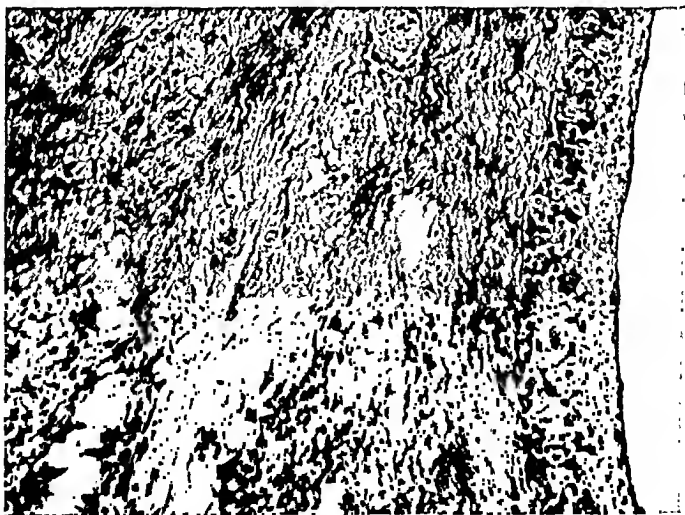


Fig. 3.—Case 1. Wall of atretic follicle showing flattened, granulosa layer with proliferation and luteinization of the theca interna. Note lutein cells in the ovarian cortex.

the ensuing five years, however, the patient was amenorrheic except for three monthly periods of bleeding one year before admission. Despite the absence of menstruation, molimina consisting of pelvic pressure and general fatigue were experienced at monthly intervals. During this time the voice changed from a definite soprano to baritone. Increasing

growth of hair about the face and trunk was noted, necessitating shaving on alternate days. There was a gain of 40 pounds in weight. In addition, for three months before admission the patient complained of frontal headaches, intermittent attacks of epigastric pain, dyspnea, nausea, and occasional vomiting.

On examination the obesity was confined mainly to the head and trunk, sparing the upper and lower extremities. The face was round and full. There was marked hirsuties of the face, chest, back, abdomen, and extremities (Fig. 4). The escutcheon was of the male type. The clitoris was enlarged to four times normal size. On pelvic examination, the uterus was normal in size and retroverted. In the cul-de-sac and to the left a fullness was felt, suggestive of ovarian enlargement. Blood pressure was 130/80 to 160/100; hemoglobin, 106 per cent; red blood

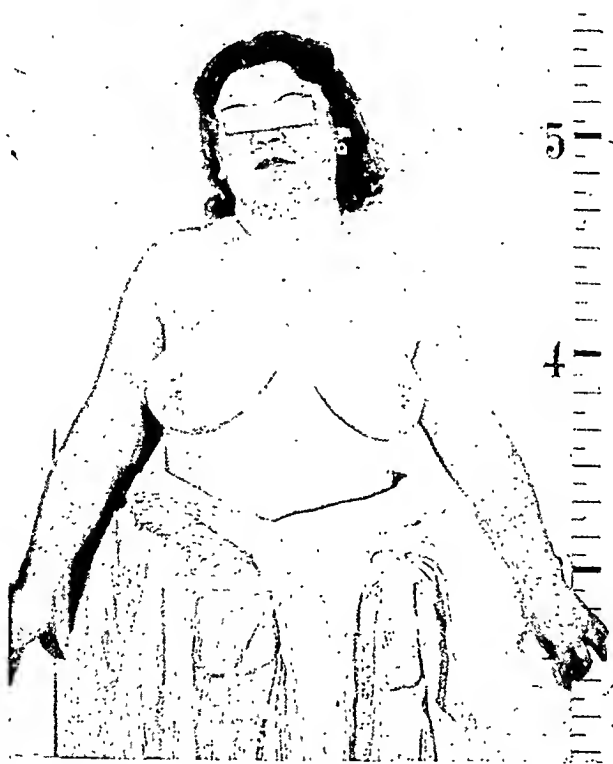


Fig. 4.—Case 2. Typical picture of virilism including obesity and marked hirsutism.

count, 5,000,000; white blood count 7,550 with normal differential count; basal metabolism, +11 per cent and +20 per cent; total proteins, 7.8 Gm. per cent; albumin, 5.7 Gm. per cent; globulin, 2.1 Gm. per cent; blood sugar, 90 mg. per cent. Blood Wassermann reaction was negative. Rehfuss test, the electrocardiogram, and visual fields were normal. Gastrointestinal series, chest x-ray, x-ray of elbows and wrists, intravenous pyelogram, x-ray of the sella turcica, and bilateral perirenal insufflation tests were all found to be negative. Because of the pelvic findings and the lack of a demonstrable lesion of the pituitary or adrenal glands, laparotomy was performed. The uterus was found to be slightly enlarged and retroverted. The left ovary was cystic, enlarged, and adherent to the lateral pelvic wall. On the right side, the appendix h

become adherent to the ovary and the latter bound down to the pelvic floor. Bilateral salpingo-oophorectomy and appendectomy were done. Convalescence was uneventful. A short time later the patient left the city, so that an adequate follow-up could not be obtained.

Gross Examination.—The right ovary measured 5 by 3.5 by 3.5 cm. in the unfixed state. On cut section numerous follicle cysts, varying from 2 to 7 mm. in diameter, rimmed the periphery (Fig. 5). No mature or recent corpus luteum was evident. The medullary portion of the

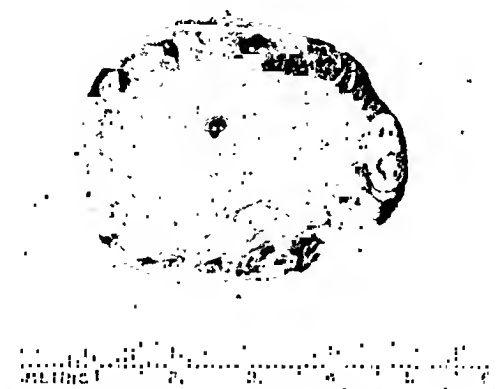


Fig. 5.—Case 2. Cross section of right ovary showing several cystic follicles. The medullary portion was of yellowish hue.



Fig. 6.—Case 2. Small groups of luteinized cells distributed irregularly throughout the parenchyma of the ovary.

ovary appeared hyperplastic and was gray yellow in color, with scattered orange yellow flecks. The left ovary was of similar size and color. Cystic follicles were not as abundant. At one pole a portion of the collapsed wall of a hemorrhagic cyst was evident.

Microscopic Examination.—Within the ovarian cortex, primordial and maturing follicles were distributed in normal numbers. The majority of the atretic follicles presented an unusual degree of perifollicular proliferation of the theca interna zone, with evidence of increased luteinizations of the theca cells (Fig. 7). Such stimulation was seen at times

about follicle cysts in which the granulosa lining had been reduced to a single, flattened layer of cells (Fig. 8). In other atretic follicle cysts, the granulosa cell lining might show increased cellular activity only in one portion of its circumference, while the theca interna cells showed more uniform hyperplasia. Scattered throughout the ovary in both

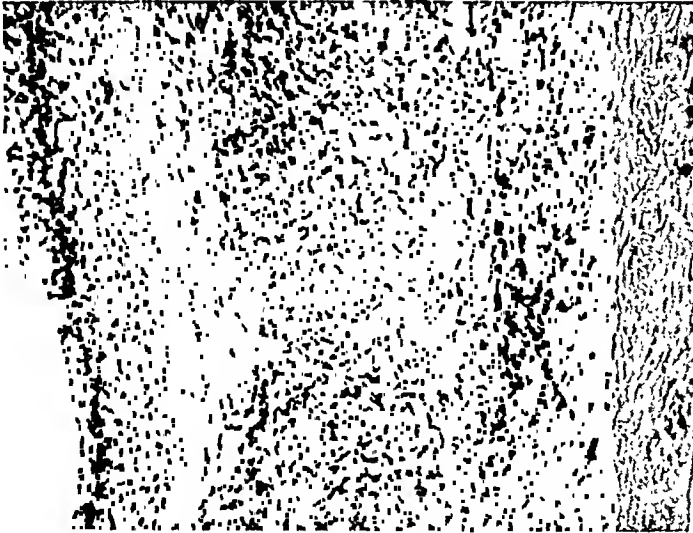


Fig. 7.—Case 2. Perifollicular, theca growth and luteinization. Note lutein cells in the cortex.

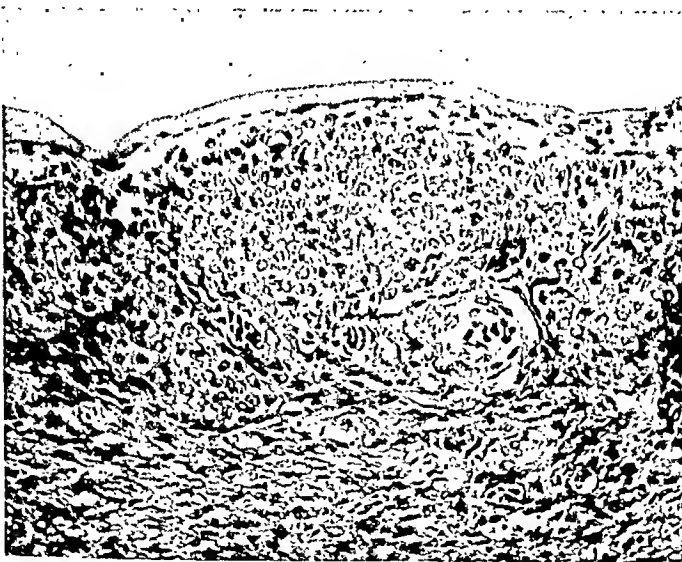


Fig. 8.—Case 2. Atretic follicle with flattened granulosa cells and unusually conspicuous stimulation of the theca interna.

cortex and medulla (Fig. 6) were irregular groups of large, vacuolated, luteinized cells, similar to those described in Case 1, but to a much lesser degree. Although many corpora albicantia were present, a recent corpus luteum could not be found.

DISCUSSION

In two cases of masculinization, luteinization of the ovaries has been found. It is apparent that this must be an unusual or even rare occur-

rence in the arrhenomimetic syndrome. It appears unlikely that the ovarian changes described are directly responsible for the clinical picture. In Case 1 there was no regression of the virilism following bilateral oophorectomy. Although a lesion of the pituitary or adrenal glands was not demonstrated clinically in the 2 reported cases, their presence or the possibility of functional alterations cannot be ruled out. Pregnanediol studies were not performed in our cases. They may be of diagnostic value in some types of hirsuties, since an excretion of pregnanediol in appreciable amounts has been found in cases of carcinoma or hyperplasia of the adrenal cortex associated with virilism.²⁰ Fortunately, there is available a report by Bergstrand in which the ovarian findings paralleled those in Case 2, and in which a complete autopsy was secured.¹ His patient was a woman, aged 42 years, whose clinical course was entirely similar to those described here. The ovaries were enlarged and yellowish. There were many atretic follicles with perifollicular zones of luteinized theca cells. At autopsy a large basophilic adenoma of the pituitary gland and diffuse hyperplasia of both adrenal glands were found. The weight of evidence, therefore, would suggest that the ovarian alterations are secondary and not directly responsible for the masculinization syndrome.

The ovarian histologic changes described in this communication are suggestive of increased gonadotropic stimulation. They are not unlike those induced artificially in the human female by gonadotropins, particularly hypophyseal extracts.⁹ The latter may produce theca proliferation and luteinization, perifollicular hemorrhage, and stimulation of granulosa and theca cells in follicles showing various stages of atresia, without, however, any evidence of increased follicle maturation, ovulation or corpus luteum formation. The excessive luteinization of theca elements in our cases, though not exactly similar may also be compared with the conspicuous theca proliferation and luteinization seen in cases of hydatidiform mole or chorionepithelioma, in which the gonadotropins are greatly increased.

It is interesting to note that similar histologic ovarian changes have also been reported in intact, suckling, female rats, following the administration of gonadotropins, and that these effects were accompanied by evidences of masculinization.^{15, 16} If injections of chorionic or equine gonadotropins are given from the sixth to the twenty-sixth day of life, follicle maturation and corpus luteum formation do not occur at that time; instead, ovarian enlargement is found to be due to perifollicular proliferation and luteinization of the theca cells, suggesting the appearance of the so-called "interstitial gland." These changes are accompanied by such masculinizing characteristics as hypertrophy of the clitoris and prepuce. Because the androgenic effects do not occur in ovariectomized animals, it was assumed that the altered ovaries were responsible for the production of an androgenic substance. However,

this inference is not entirely warranted, since the function of the adrenals may also have been affected.

SUMMARY

The syndrome of masculinization in the female, attributed to pituitary basophilism or adrenal cortical lesions, usually includes regressive changes in the ovaries. At times, however, as evidenced by the two cases described in this report, there may be bilateral ovarian enlargement, due to excessive perifollicular proliferation and luteinization of the theca cells and diffusely scattered luteinized cells within the ovarian parenchyma.

The ovarian effects are suggestive of increased gonadotropic stimulation and are probably secondary. It does not appear that they are responsible for the production of the masculinization syndrome.

In the clinical investigation of virilism the presence of an ovarian enlargement has been and should be regarded as suspicious evidence of a possible arrhenoblastoma or adrenal rest neoplasm of the ovary. In view of this report, a third possibility exists, namely, enlargement of the ovary due to diffuse luteinization. It may be possible to decide, at operation, by incision of the ovaries, whether or not tumor is present. If, in young patients, tumor can unequivocally be ruled out by this device, one or both ovaries may be left in situ.

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THE CYTOLOGIC RELATIONSHIP OF THE WALTARD CELL REST TO THE BRENNER TUMOR OF THE OVARY AND TO THE PSEUDOMUCINOUS CYSTADENOMA

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MOST authorities agree that Brenner tumors of the ovary probably have as their anlagen the cell rests described by Walthard in 1903. In addition, the occasional finding of Brenner tumors in the walls of pseudomucinous cystadenomas of the ovary, and the more frequent finding of pseudomucinous epithelium in Brenner tumors and Walthard rests, have been cited as indications that at least a portion of the pseudomucinous cystadenomas may have their origin in Brenner tumors. If these inferences are true, one might expect to find certain cytologic as well as architectural features common to all three structures. It is the purpose of this communication, first, to describe more minutely the cells making up the Walthard rests, the Brenner nests, and the pseudomucinous cystadenomas of the ovary, and, second, to indicate certain points of similarity. Upon the basis of these descriptions it seems possible to offer further indication of their common origin, and also to suggest a third criterion for the diagnosis of the Brenner tumor.

A detailed review of the literature concerning these structures seems unnecessary, since it is considered in all recent textbooks and articles dealing with the subject.

The *Walthard rest* is a small collection of cells which may be found in the cortex or hilus of the ovary, or beneath the serosa or within the mesosalpinx of the Fallopian tube. The rests are of two types, the solid and the cystic. In the cystic type the central portion of the rest is occupied by a clear space which is said to contain mucin or pseudomucin, colloid, or mixed material. The cystic cavity is ordinarily lined by from one to ten or more layers of cells. There appears to be no accurate estimate of the frequency of these rests except that of Muller, who found them in 12 per cent of 251 adnexa examined. The origin of the Walthard rests is obscure. They are stated variously to arise from the coelomic epithelium of the developing embryo, from an inflammatory reaction of the peritoneum, from the germinal epithelium and from numerous other structures. The first named is probably most widely accepted.

The *Brenner tumor* is one of the group of rare ovarian tumors, less than 150 of them having been reported. They may occur in women of

all ages, but are said to be more common in middle or late middle age. They may vary in size from a few millimeters in diameter to more than seven kilograms in weight. Their diagnosis is based wholly upon microscopic findings, since they have no gross or clinical characteristics which are peculiar to these tumors alone. Histologically, two criteria have been mentioned as essential for their diagnosis. These are, first, the presence of small characteristic cell nests which are, second, surrounded by a zone of fibrous tissue. The latter may be sufficiently extensive to give the gross impression of a fibroma. Two types of Brenner tumor have been described, though intermediate and mixed varieties are not uncommon. The first of these is the solid type, in which the cell nests are composed of rather closely packed cells. The second is the cystic type, in which the central portions of the nests are occupied by clear spaces. These spaces may be empty, or they may be filled by large nondescript cells, or by pseudomucin, or mixed material.

The *pseudomucinous cystadenoma* is sufficiently well known that its characteristics need not be mentioned here.

The reason why the Walthard rests were first incriminated as precursors of the Brenner tumor is not entirely clear. Perhaps it is because the Brenner tumors bear a very close qualitative resemblance to the rests; the major anatomic difference appears to be quantitative. The chief objection to this theory of the evolution of the Brenner tumor is that the tumors have never been observed in the tube, where the rests are commonest. The customary explanation of this discrepancy is that the tube is notorious for its indifference to tumor growth of all kinds despite the presence of tissues which in other sites may give rise to tumors of enormous size and variation. The fundamental reason for this indifference will probably be found only when the precise conditions necessary for tumor growth in any site are determined.

The observation has been made that in occasional instances the cystic Walthard rests may be lined in part by pseudomucinous epithelium, the latter merging imperceptibly with that of the heavier portion of the rest wall. This has also been observed in some of the cystic Brenner tumors and, in addition, true Brenner tumors have been reported in the walls of pseudomucinous cystadenomas. The latter finding is cited in support of the contention that in occasional instances, the cystadenomas may arise from previously existing Brenner tumors. This purported evolutionary relationship is indeed highly circumstantial, since it is impossible to establish it upon a sound experimental basis. Additional observations may strengthen or weaken this hypothesis, but will probably fall short of absolute proof. The material presented herewith adds weight to the belief that the Walthard rests, Brenner tumors, and pseudomucinous cystadenomas are fundamentally related to one another. Precisely what this relationship is cannot be stated.

MATERIALS AND METHODS

Tubes, Ovaries, and Cystadenomas.—This material consists of single microscopic sections of 350 consecutive normal Fallopian tubes and of 100 essentially normal ovaries, together with at least three slides each of 50 benign, uncomplicated pseudomucinous cystadenomas.

Brenner Tumors.—The Brenner tumor material available for study consists of 18 tumors. This is not a large number. It comprises, however, something more than one-tenth of the Brenner tumors which have been reported. Of these, 11 are among the slide collection of the Laboratory of Gynecological Pathology of the Johns Hopkins Hospital, and were studied with the kind permission of Dr. Emil Novak. Four tumors were made available through the kindness of Dr. W. C. Danforth of Northwestern University. The remaining three were observed in the pathologic laboratory of the Sloane Hospital for Women; they are the only Brenner tumors which have been observed here in the nine years since they were first clearly described and classified by Robert Meyer. During this time more than 10,000 obstetric and gynecologic cases have been studied. These three tumors have not been reported hitherto. The first tumor, observed in 1933, was of the solid type. The patient was a 38-year-old colored female, who complained of menorrhagia. At operation the associated pathology was found to consist of fibromyomas of the uterus, pelvic peritoneal adhesions, and chronic salpingitis. The ovaries were normal in appearance except for numerous filmy adhesions which enveloped them. The Brenner tumor was an incidental microscopic finding. The tumor is illustrated in Fig. 2. The second tumor, seen in April, 1940, was of the semisolid type. It is shown in Fig. 4. The patient was a 36-year-old colored female who complained of menorrhagia and metrorrhagia. At operation associated pathology was found to consist only of fibromyomas of the uterus. The adnexa were grossly normal. The Brenner tumor was an incidental microscopic finding. The third tumor, observed in October, 1940, was mixed, containing solid and cystic nests in approximately equal proportion. The patient was a 41-year-old white female who complained of menorrhagia. The associated pathology consisted of a placental polyp, myometritis, and chronic salpingitis. The adnexa were covered by filmy adhesions. The Brenner tumor was an incidental microscopic finding.

In the instances of the Fallopian tubes and ovaries, a careful examination was made for the presence of Walthard rests. The Brenner tumors, cystadenomas, and the entire series of Walthard rests were then studied with reference to cellular detail and, more precisely, to nuclear detail.

All of the routine slides are stained with hematoxylin and eosin. All of our own material was fixed by the Zenker's technique. In many instances blocks were recut so that special stains might be made.

RESULTS

In the *tube*, almost four times as many cystic rests were found as solid ones. In occasional instances the decision as to whether cystic or solid was difficult due to the fact that some were mixed, others intermediate. The rests occurred with approximately equal frequency beneath the serosa of the free edge of the tube, and within the mesosalpinx.

TABLE I. WALTHARD RESTS

	NUMBER OF ROUTINE SECTIONS EXAMINED	TOTAL WALTHARD RESTS FOUND		CYSTIC WALTHARD RESTS		SOLID WALTHARD RESTS		AVERAGE AGE OF PATIENTS
		NO.	% OF NO. EXAMINED	NO.	% OF TOTAL RESTS	NO.	% OF TOTAL RESTS	
Fallopian tube	350	56	16	43	77	13	23	41
Ovary	100	5	5	4	80	1	20	43

The average age of the patients is indicated. The oldest patient in this series of 56 cases was 53 years, the youngest 15. Six patients were negroes, the remainder white. The most common associated pathologic findings included fibromyomas of the uterus (29 cases), endometriosis (6 cases), and adenomyosis (3 cases). Five patients were sterilized by resection of the tubes; 3 of these were pregnant at the time of operation. At least 21 of the patients were parous, and at least 12 nulliparous.

When the solid tubal rests are examined with the very low power objective of the microscope (30× magnification), they give the impression of a nest of very closely packed basophilic cells. With a little higher magnification (90×), the cellular detail is still not evident, but one sees readily that the structure is surrounded by a zone of fibrous tissue of varying thickness. With the high dry objective (400×) or, preferably, with the oil immersion lens (900×), the details become apparent. The most striking feature of the cells is the nucleus, which is not simply round or ovoid, as it has been described, but in addition is seen to be marked or "tagged" in a specific manner. This marking consists of a tiny groove or fold which traverses the long axis of the nucleus in such a manner as to remind one of a coffee bean, or a kernel of puffed wheat. In many of the rests this characteristic marking is present in approximately 9 of 10 nuclei, being evident as a straight, bold line through the long axis, dividing the nucleus into two almost equal halves. As nearly as can be ascertained, this basic pattern is characteristic of one of the flat surfaces of a healthy, nondegenerate nucleus. In these instances the nuclear material is seen to be very finely granular and to contain, generally, one or two nucleoli. When two nucleoli are present, one usually appears upon either side of the dividing groove. In some cases the nucleoli take a pink stain. In rests such as these the outlines of the individual cells are generally not apparent, only a very fine reticulum appearing to lie between the nuclei.

Within the same rest numerous variations of the basic nuclear pattern may be seen. These appear to depend first upon the angle from which the cell is viewed, and second, upon the stage of development or regression which the rest has reached. Not infrequently the groove or

fold appears to be oblique, giving the impression that the marked surface of the nucleus is viewed from an angle. In other instances some of the nuclei may be shaped like coffee beans which are viewed toward one pole. Occasionally the nucleus is long and ovoid, as though viewed from the side.

The second type of variation, believed to be of a regressive nature, is seen occasionally in the solid rests, but far more commonly in the cystic or intermediate variety. The most striking alteration of this type occurs in the nuclei, with regard both to their distribution and morphology. At first glance it is readily evident that the individual nuclei are much farther apart than in the rests described above. The nuclei show no significant alteration in size, but may be extremely variable in shape and detail. A small proportion of the nuclei (at least one in ten) are

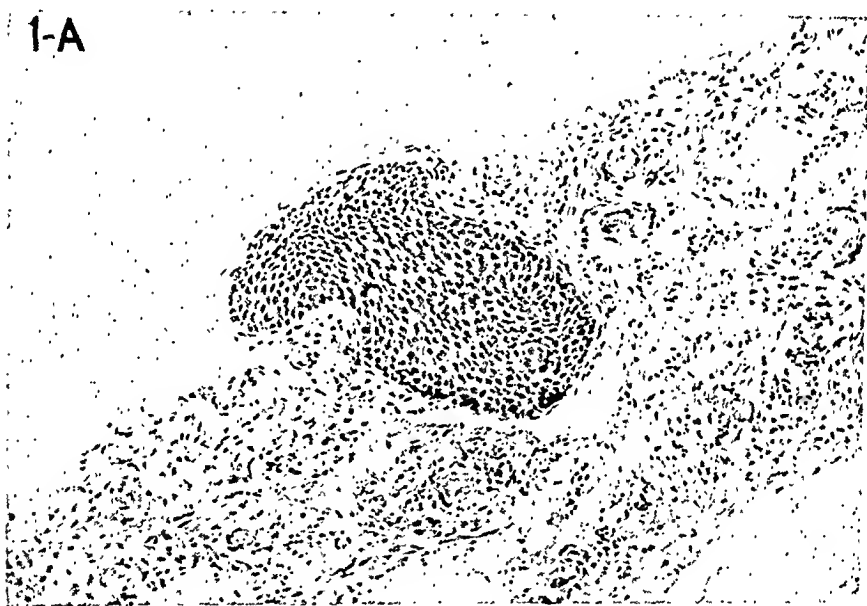


Fig. 1.-A.

Fig. 1.—A, Solid Walthard rest of tube (approximately 90 \times); B, oil immersion photomicrograph, same rest (approximately 900 \times); C, drawing of same field as B, to indicate detail which is not evident in B, since in the latter only occasional cells are in focus at the same time.

of the basic type. The remainder show various deviations. These are manifest especially as shortening, irregularity or complete absence of the median fold, loss of the granular quality of the nuclear material, absence or infrequency of nucleoli, and irregularity or wrinkling of the nuclear outline. In addition, the cell outlines in instances such as this are generally quite distinct, the cells now being evident as round, ovoid or polyhedral in shape, and of large size. The cytoplasm is clear and highly refractile, being seen only as a clear space which surrounds the nucleus.

Although nuclear deviations are more common in rests of the cystic or intermediate type, they may be seen occasionally in solid ones.

Furthermore, in many of the cystic rests, the great majority of the cells are of the basic type. Generally the more peripheral cells are typical, while the ones near the central cavity show one or more of the degenerative changes indicated above. In occasional cystic rests, the heavier

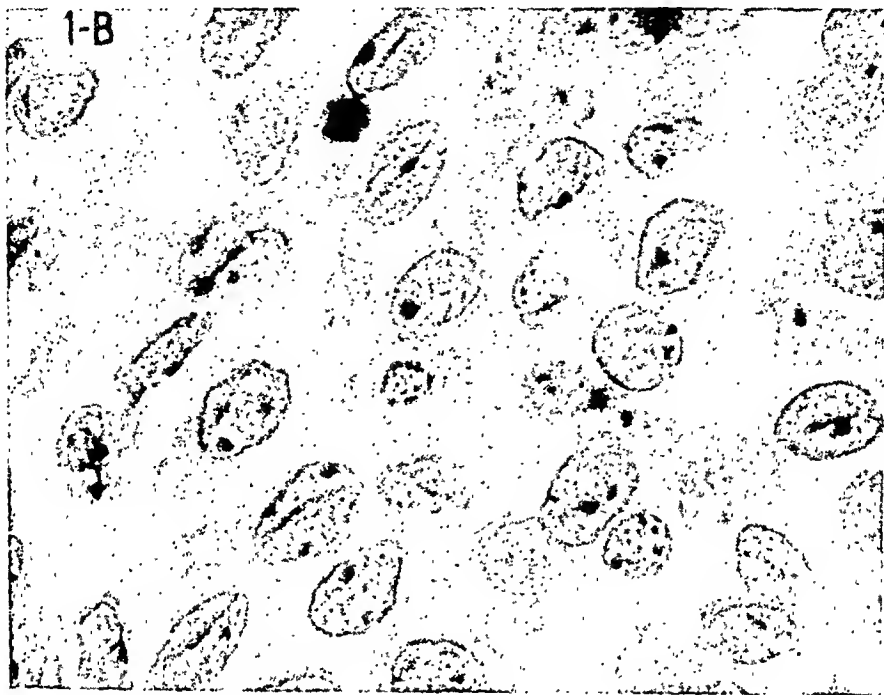


Fig. 1.-B.



Fig. 1.-C.

portion of the cyst wall may be seen to fade gradually into a single layer of epithelium which is indistinguishable from that which is typical of the pseudomucinous cystadenoma. Others may be lined in part by a single layer of squamous epithelium which shows no resemblance to the basic cell type observed in the remainder of the rest.

In the ovary the incidence of Walthard rests was far less. This does not indicate necessarily that they occur here with less frequency, but rather suggests that our routine sections may not have been taken through a portion of the ovary which would include them. When seen, ovarian rests were found in the ovarian stroma a short distance below the germinal epithelium. It is of interest that the nuclear peculiarities of the rests distinguish them from tangentially sectioned ova. In two

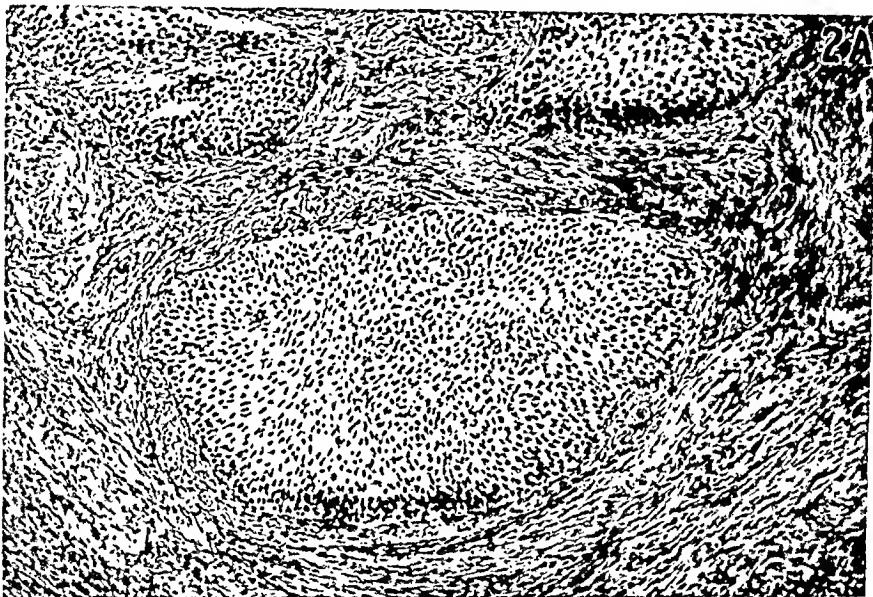


Fig. 2.-A.

Fig. 2.—A, Solid Brenner tumor (90 \times); B, oil immersion photomicrograph, same cell nest (900 \times); C, drawing of same field as in B. Fig. 1 was a rest selected to show similarity of rest to Brenner tumor, and to correspond in general to the solid tumor.

instances, tangential section of the germinal epithelium showed the latter to be made up of cells resembling the basic type previously described. These are not included in the five rests entered in Table I, since they do not conform to the definition of Walthard rests. The similarity of structure does suggest, however, that they are in some wise similar to the true rests discussed. Of the patients showing ovarian rests, 4 were white, 1 was a negro; 3 were parous, 2 nulliparous; none had reached the menopause. Associated pathologic findings included endometriosis (two cases) and fibromyomas of the uterus (three cases). One of the latter was complicated by chronic salpingitis.

Brenner Tumors.—The general architecture of the Brenner tumor has been outlined above. In all instances but one, in which faulty fix-

tion had obscured the cellular structure of the entire tumor, the Brenner tumors examined were seen to be strikingly similar in cytologic detail to the Walthard rests which were described above. The nuclei contain the same fold or groove. The same nuclear variations are present, being accompanied by the other cytologic deviations mentioned previously.

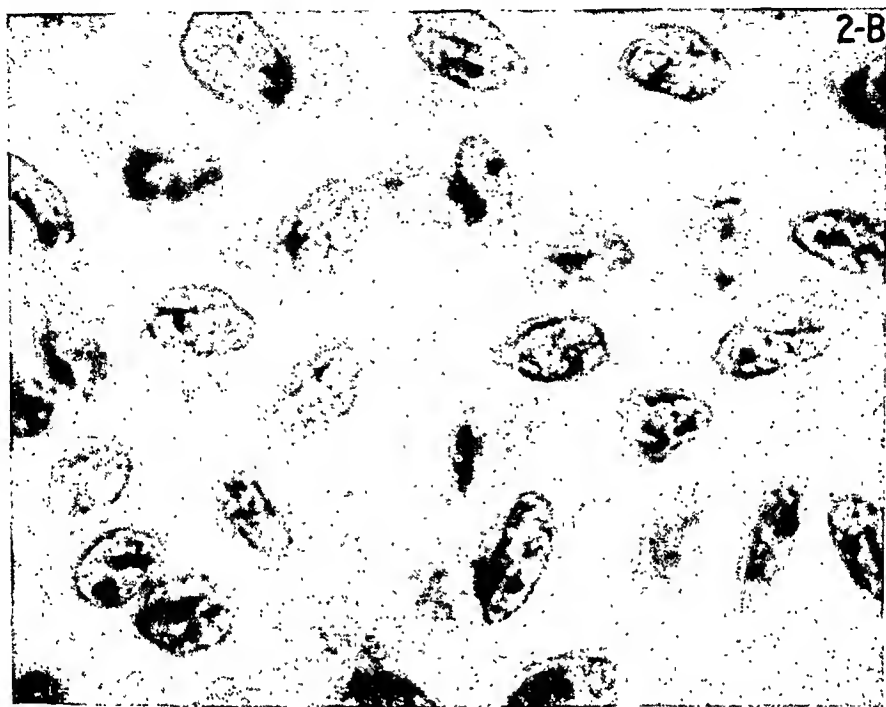


Fig. 2.-B.



Fig. 2.-C.

The incidence, distribution, and size of the nucleoli are similar. Only one primary difference has been observed between the cytologic aspects of the Walthard rests and the Brenner tumors: the nuclei may show slightly more variation in size. *In all of the Brenner tumors the basic nuclear type appears in sufficient frequency to be regarded as a funda-*

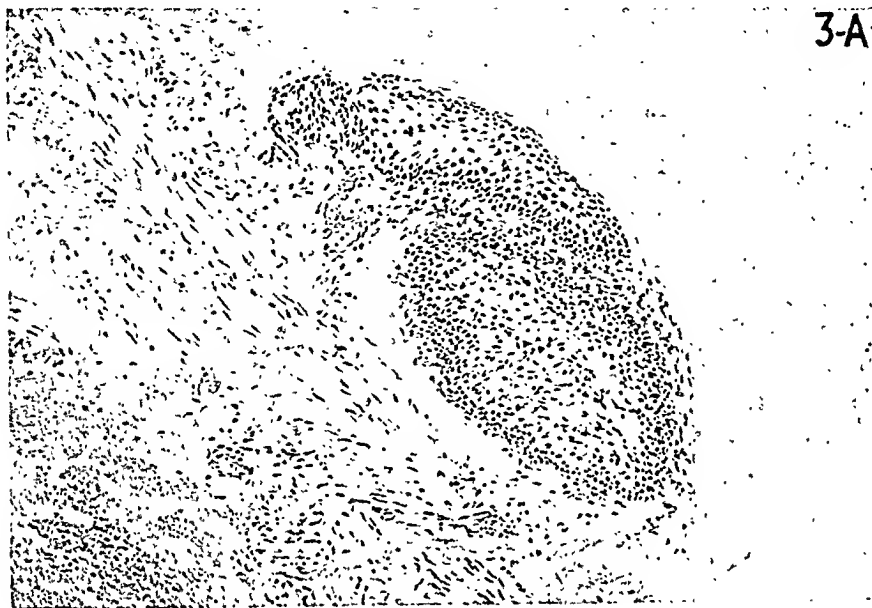


Fig. 3.-A.

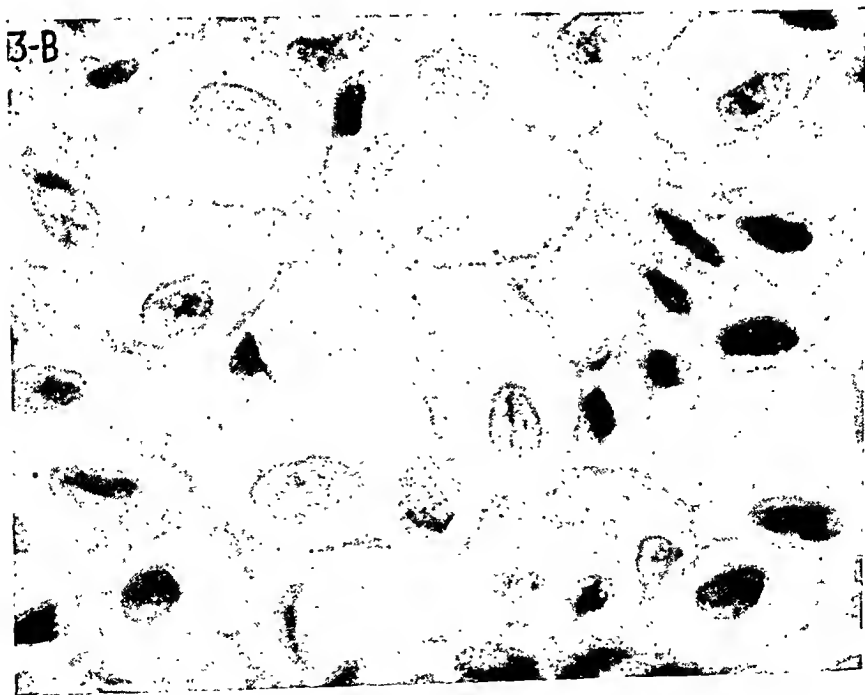


Fig. 3.-B.

Fig. 3.—A, Semisolid Walthard rest of tube (90X); B, oil immersion photomicrograph, same rest (900X).

mental characteristic. Figs. 1 to 4 illustrate the close cytologic similarity of the Brenner tumor to the Walthard rest.

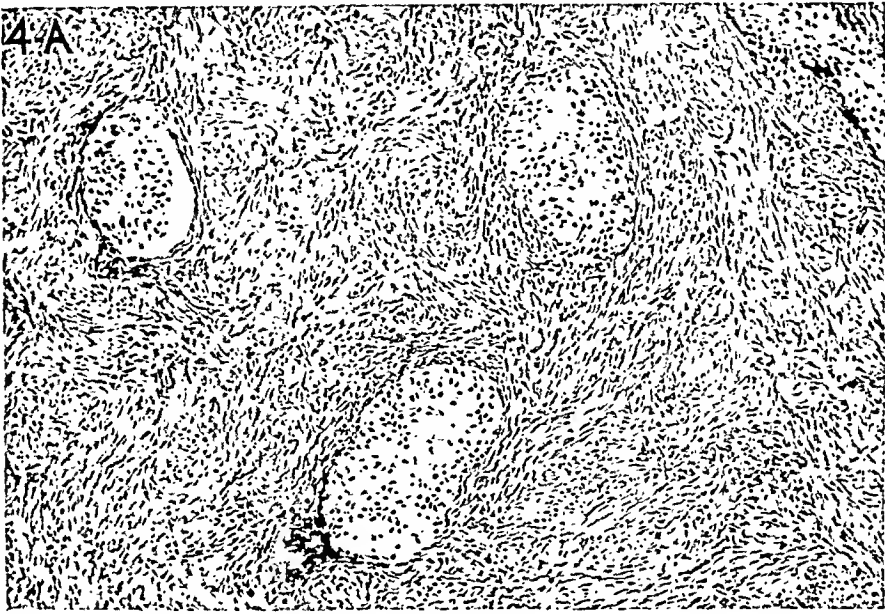


Fig. 4.—A.

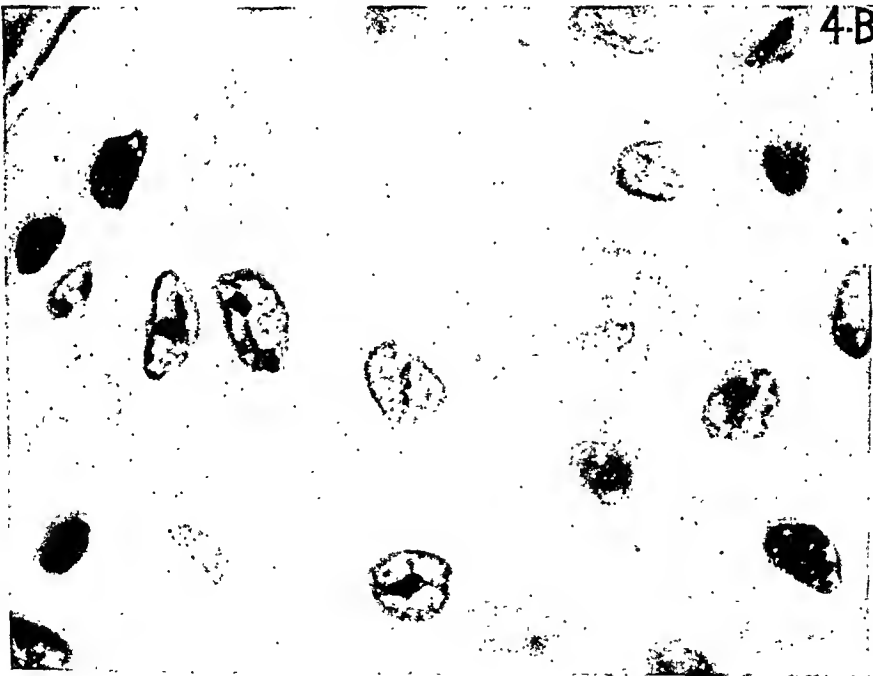


Fig. 4.—B.

Fig. 4.—A, Semisolid Brenner tumor (90X); B, oil immersion photomicrograph same nest (900X). (Compare with Fig. 3.)

Pseudomucinous Cystadenomas.—No Brenner tumors were found in careful examination of the pseudomucinous cystadenomas. It will be recalled that the characteristic cell of this tumor is of tall columnar type, with clear refractile cytoplasm, and deeply staining, small, often

creseent-shaped nuclei which are located close to the basement membrane. Most tumors, however, contain one or more areas where the epithelium is somewhat shorter, the nuclei ovoid in shape, and somewhat more lightly staining. Many of the cells in these areas approach a euboidal, or even polyhedral shape. Novak states that cells such as this are of the immature type, and that they evidence active proliferative activity. *It is in this group of cells that one finds the only common cytologic link between this tumor and the Brenner.* In many of these immature cells the nuclei show a striking and rather precise similarity to those which have been termed the basic nuclear type. This similarity is especially evident where the epithelial layer has been cut tangentially, as here the nuclei may be seen in a relationship to one another which is like that noted in the other two situations. In occasional instances where the base of one of the cyst lobules is cut across, the cells appear to be embedded in a heavy zone of fibrous tissue and thus bear a strong resemblance to the Brenner cell nest and the Walthard cell rest.

Special stains have revealed no information which is not evident by the routine hematoxylin and eosin stains. Iron hematoxylin stains have in some instances accentuated the nuclear details, but add no new information. Stains for mucin and pseudomucin have been rather disappointing in the Walthard rests and Brenner tumors. In occasional instances the central portion of a cystic rest is seen to take a deep stain, but ordinarily the cyst contents have not withstood the processes of fixation and dehydration.

It is emphasized that the nuclear detail is readily evident only if the material is properly fixed and dehydrated, and if the hematoxylin stain is of the proper intensity. The nuclei are not distinguishable from any other nuclei if the stain is too deep, or if a light of low intensity is used, or if they are studied only with the low power objective of the microscope.

COMMENT

The techniques used give no information as to the nature or cause of this nuclear peculiarity which is common to the Walthard rest, the Brenner tumor, and certain of the pseudomucinous cystadenomas. A search of the literature dealing with Walthard rests and Brenner tumors reveals no mention of this detail of nuclear morphology. It appears not to be an artefact, since it is seen with such striking similarity not only in our own material, but in that obtained from two other laboratories, all three of which employ different fixing and dehydrating agents. It is possible that it may be due simply to folding. Why this should occur not only in the solid collections of cells, where folding might conceivably be due to crowding, but also in the cystic or semi-cystic rests and nests, where there is not the slightest evidence of nuclear

crowding, cannot be stated; nor can one state why cells such as these do not occur with greater frequency in other densely cellular tissues. The possibility therefore arises that these cells may be of a specific type, entirely separate and apart from any ovarian or tubal cells heretofore described. To be sure, one must consider such a possibility with caution, since similar cells may be seen in structures other than those herein considered. For example, isolated cells of like configuration may be found occasionally in the epithelium covering the mucosal folds of the Fallopian tube, in the ovarian stroma, and elsewhere. In addition, of 8 granulosa cell carcinomas examined, one contained several circumscribed areas made up of cells which were indistinguishable from those described here. One of the remaining 7 contained occasional such cells, whereas the cells making up the other 6 were of the characteristic granulosa cell type. In the latter, many of the cells were folded, but their outlines were sharply angulated and irregular, and of varying shape and size. In the first instance, the question arises as to whether the tumor may be of a mixed type, or whether, under certain circumstances, the cells making up the granulosa cell carcinoma may assume characteristics similar to those described. It is worthy of mention, however, that with the single exception of the tumor mentioned above, I have never seen these cells in such profusion or with precisely the same relationship to one another as in the tissues discussed here. Of incidental interest is the fact that the cells making up the rete ovarii and the epoophoron tubules are not of the basic type herein described. This might be considered as evidence against the hypothesis of Schiller that Brenner tumors may arise from these structures.

In discussing with various authorities the possibilities as to the identity of these cells, the most significant opinion received was that of Dr. A. C. Ivy, who calls attention to the striking similarity of the nuclei to those of Sertoli cells. Sertoli's cells, it will be recalled, are found in the epithelium of the seminiferous tubules of the adult testis. Their function is supportive and nutritive. They have no endocrine function, as evidenced especially by the fact that the seminiferous tubules of the cryptorchid testis are composed only of these cells. Of especial interest is the development of the Sertoli cells from indifferent epithelial cells of the undifferentiated embryonal gonad. Further exposition of the possible relationship of the basic cell type herein described to the Sertoli cell is beyond the scope of this paper. However, a course of investigation is suggested which may solve the riddle of the histogenesis of the Walthard rest, the Brenner tumor, and at least a portion of the pseudomucinous cystadenomas of the ovary.

SUMMARY AND CONCLUSIONS

Walthard rests are a common finding in the normal Fallopian tube. They occur, but appear to be less common, in the ovary.

Walthard rests and Brenner tumors bear a strong resemblance to one another, not only in intrinsic architecture, but also, and more especially, in nuclear detail. The basic nuclear type of each is readily identifiable by the presence of a median groove or fold. The deviations from this basic type are described. Though by no means limited to the tissues in question, this nuclear peculiarity is sufficiently constant to be regarded as a fundamental characteristic of both the Walthard rest and the Brenner tumor. Furthermore, its presence in both structures appears to strengthen the hypothesis that they may be derived from the same tissue. The similarity of this nucleus to that of the testicular Sertoli cell is worthy of note.

The presence of the basic nuclear type in many pseudomucinous cystadenomas is of interest in considering the possibility that a small proportion of these tumors may be derived from Brenner cell nests.

ADDENDUM: Since this paper was submitted, a fourth Brenner tumor has come to our notice. The patient was a 41-year-old Negress who complained of menorrhagia and metrorrhagia of two years' duration. Associated pathologic findings included fibromyomas of the uterus and salpingitis isthmica nodosa. The Brenner tumor was an incidental finding. The tumor measured 0.6 cm. in diameter, and was of the solid variety. The cellular detail conforms with the description given above.

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THE RELATIONSHIP BETWEEN LATE PRENATAL HEMOGLOBIN LEVELS AND FEBRILE PUERPERAL MORBIDITY

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THAT the course of the puerperium is influenced by the amount of blood lost at the time of delivery, has been emphasized by Peckham and Kuder,¹ Pastore,²⁻⁴ and Reich,⁵ among others. Pastore, whose work is of particular interest, found an association between the amount of blood lost in relation to the size of the individual and the post-partum blood cell volume. He found further a distinct relationship between each of these factors and the incidence of puerperal febrility. While he does not mention adjustments for complications, trauma, and operative interference, factors which may simultaneously affect both bleeding and exposure to infection, it is unlikely that his findings are explainable on this basis alone.

Assuming the post-partum physiologic concentration of the blood to be a fairly uniform process, any differences in the puerperal blood content would depend upon both the blood status at term and the blood loss experienced at delivery. The relationship between the extent of this loss and the occurrence of post-partum morbidity having been demonstrated by Pastore, the question arises whether the prenatal blood status, as routinely determined, shows a similar relationship to the puerperal course.

It has repeatedly been observed that, in a large proportion of all pregnancies, there is a definite decline in hemoglobin values, often to low levels. Opinions differ as to the extent that this is attributable to physiologic hydremia, on the one hand, or to true hypochromic anemia on the other. In any event, the functional capacity of the blood may well vary with its content per unit of volume, however, produced. The practical importance of examining this content, as a prenatal routine depends upon: (1) Is the information useful in the management of pregnancy? (2) May a simple procedure, such as a hemoglobin determination, serve as an index? The purpose of this study is to determine, if possible, whether the likelihood of post-partum fever varies with the ante-partum hemoglobin level, despite certain inaccuracies of the test, and regardless of the differing interpretations respecting anemia. The material reviewed is taken from the records of normal deliveries on the

obstetric service of the Johns Hopkins Hospital, over the three-year period, Sept. 1, 1937, to Aug. 31, 1940.

METHOD AND CONDITIONS OF STUDY

In view of the lack of uniformity in the prenatal records of private cases, these were considered unsuitable for the purpose. Since in primiparous labor trauma is quite varied and artificial delivery frequent, it seemed desirable also to limit the study to multiparas.

The routine prenatal practice of the clinic included hemoglobin readings (Sahli) at the time of registration, and again within the "last month." The "last month" reading falls actually within twenty-eight days of labor in only about one-half of the patients. In hospital deliveries blood loss was estimated or measured with about equal frequency. Checks indicated that estimates are approximate within 50 c.c. Blood loss in homes was almost always estimated. During the puerperium, temperature was recorded at four-hour intervals in the wards, and once daily in the home. Excluding the first day, if the temperature reached 100.4° F. or more on any two days, the case was coded as "febrile"; if on only one day, as "one-day fever."

Patients with abnormal conditions during pregnancy, possibly affecting both blood content and temperature, were excluded, as were patients who had premature labor, artificial delivery, induction, tamponade, and similar manipulations not fairly common to the entire group. Also discarded were afebrile patients whose records covered less than eight days, and patients receiving transfusion, except when given after the onset of fever. Because of marked differences in the incidence of fever in negro and white patients, the two were separately tabulated. Further separation was made between confinements in the home and in the hospital. Home cases were included since, in a dual service, the hospitalized group might not be completely representative of all patients enrolled.

This method of selection seems to provide a group of cases in each category that is reasonably homogeneous with respect to those obvious extrinsic variables which affect the probability of febrile puerperiums.

FINDINGS

The records of 2,018 consecutive, normal parous pregnancies, with spontaneous term deliveries, were selected and abstracted according to the foregoing definitions. They are distributed into four principal categories, with incidence rates of febrile puerperiums, as follows:

Hospital cases	470 negroes	51 febrile	10.9%
	520 whites	35 febrile	6.7%
Home cases	741 negroes	44 febrile	5.9%
	287 whites	9 febrile	3.1%
Total cases	<u>2,018</u>	<u>139</u>	<u>6.9%</u>

For each place of confinement, negroes experience febrile puerperiums about twice as frequently as do white individuals. This conforms to the experience covering all cases on this service. Among hospital patients, whose temperature is taken more frequently, the incidence of fever is double that for home patients of corresponding color, in this particular series. This differs in degree from the general experience of the service, where the ratio is about 5 to 1. The discrepancy is attributable to the exclusion, from the series, of complications and operative procedures.

It is felt that in general the late prenatal hemoglobin status is reasonably well evaluated if observations are made within four weeks of labor. In the series studied, record of such examination was found in 1,001 patients, about half of the total. In each of the four principal categories, comparisons of febrility rates for patients with known and with unknown hemoglobin levels showed no differences that were statistically significant. The sample of 1,001 cases may therefore be considered as representative of the whole group studied.

In Table I these 1,001 cases are divided by color, and distributed by grouped hemoglobin values. The distributions are obviously different as between white individuals and negroes. Less than 14 per cent of the

TABLE I. LATE GESTATIONAL HEMOGLOBIN GROUPING OF 1,001 NORMAL MULTIPARAS, SPECIFIC FOR COLOR

HEMOGLOBIN GRAMS PER 100 C.C.	NUMERICAL DISTRIBUTION		PER CENT DISTRIBUTION	
	WHITE	NEGRO	WHITE	NEGRO
6.5- 8.9	14	66	3.2	11.6
9.0- 9.9	45	106	10.4	18.7
10.0-10.9	117	200	27.0	35.2
11.0-11.9	111	137	25.6	24.1
12.0-14.5	146	59	33.7	10.4
Totals	433	568	99.9	100.0

TABLE II. PUERPERAL FEBRILITY RATES FOR VARYING LATE PRENATAL HEMOGLOBIN LEVELS

From records of 1,001 normal multiparas, spontaneous term deliveries, showing number of cases, and percentage with febrile puerperiums, according to place of confinement and hemoglobin values within last four weeks of gestation.

HEMOGLOBIN GRAMS PER 100 C.C.	HOSPITAL CASES		HOME CASES		TOTALS	
	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE	NO. OF CASES	% FEBRILE
6.5- 8.4	22	27.3	21	14.3	43	20.9
8.5- 8.9	13	23.1	24	16.7	37	18.9
9.0- 9.4	36	16.7	47	8.5	83	12.0
9.5- 9.9	30	16.7	38	13.2	68	14.7
10.0-10.4	95	10.5	100	7.0	195	8.7
10.5-10.9	58	6.9	64	3.1	122	4.9
11.0-11.4	66	7.6	94	2.1	160	4.4
11.5-11.9	44	4.5	44	2.3	88	3.4
12.0-12.4	84	2.4	59	0.0	143	1.4
12.5-14.5	33	3.0	29	3.4	62	3.2
Totals	481	9.2	520	5.6	1,001	7.3

white patients had under 10.0 Gm. of hemoglobin per 100 c.c. of blood, as compared with 30 per cent of the negroes. Over three times the proportion of white patients as of negroes reached term with hemoglobin levels of 12.0 or higher.

Per cent
febrile
puerperia

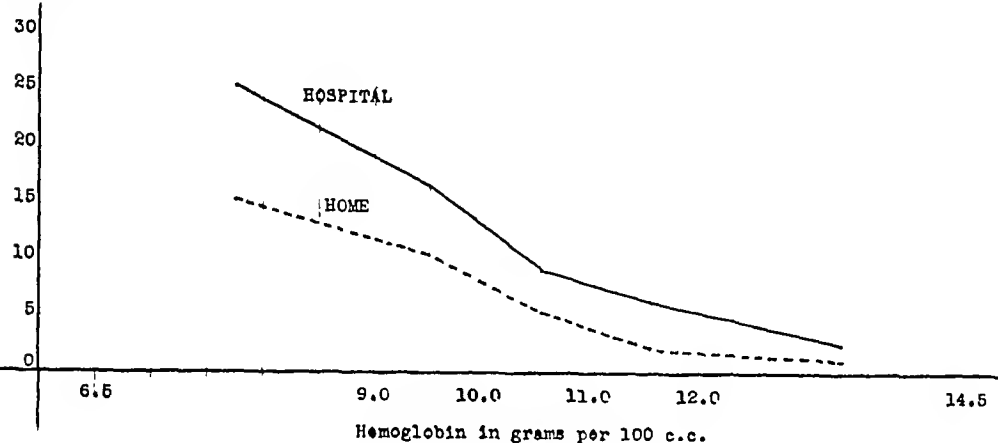


Fig. 1.—Relation of late prenatal hemoglobin level to puerperal febrility in 1,001 normal multiparas, by place of confinement (Table III).

Per cent
febrile
reactions

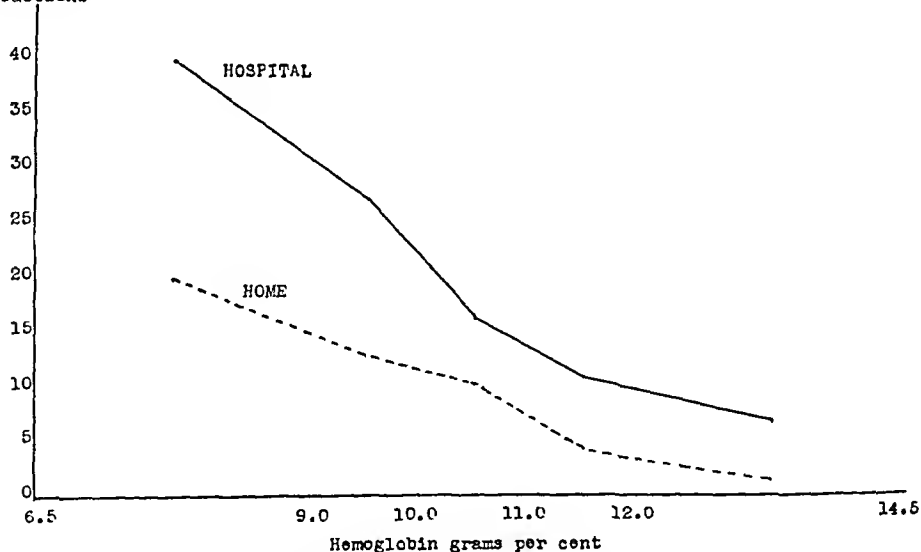


Fig. 2.—Relation of late prenatal hemoglobin level to puerperal febrile reactions, including "one-day fever" in 1,001 normal multiparas, by place of confinement (Table IV).

Table II shows the same sample distributed by place of confinement and by late prenatal hemoglobin levels, in one-half-gram steps, with the febrility rates for each subgroup. The marked decline of fever incidence with ascending blood values is shown graphically in Fig. 1. The same consistent relationship is reflected when the data are subdivided accord-

ing to color. Table III shows this analysis summarized by grouping the hemoglobin values into broader classes.

Summarizing these tabulations, those patients with prenatal hemoglobin values under 9.0 Gm. had febrility rates of 25.7 per cent in hospitals and 15.5 per cent in homes, whereas those with values of 12.0 Gm. or more had rates of 2.6 and 1.1 per cent, respectively. The incidence shows a consistent trend downward with ascending intermediate hemoglobin levels throughout all the tabulations. There are but rare interruptions, incident to small samples in the smaller subdivisions of Table II.

The sample was then examined to determine whether a relationship of this order is reflected by "febrile reaction" rates, when cases of "one-day fever" are added to those of conventionally defined morbidity. The analysis is given in Table IV and shown graphically in Fig. 2. Rates for corresponding hemoglobin levels differ from those of Table III in magnitude, but the internal arrangements are strikingly similar. Thus, either by the usual standard of puerperal febrility or by including all one-day fevers, the inverse relationship to late gestational hemoglobin content, per unit of blood, seems evident.

Especially noteworthy is the steady decline of febrility with ascending prenatal hemoglobin, between and beyond levels of 10.0 and 12.0 Gm., the range embracing values usually considered "satisfactory" or "normal."

The influence of blood loss at delivery is a factor that also must be considered. In these records bleeding is expressed in terms of absolute quantity, without regard to the size of the patient. The observation was recorded in 2,015 cases, of which 1,027 are home deliveries with estimated blood loss. Of 988 hospital deliveries, 60 per cent have estimates and 40 per cent have measurements. The proportion of measurement of blood loss was about the same among those of known and of unknown late hemoglobin status.

Febrility rates for varying amounts of blood loss at delivery are given in Table V. For comparison, the 396 hospital deliveries with measured blood loss are shown separately. Fever rates in this group closely approximate rates within the whole hospital group. For the purpose of separating cases into broad classes of blood loss, the inclusion of estimates seems acceptable.

There is no discernible trend of fever incidence with rising losses of blood in ranges below the "hemorrhage" level, but a marked rise occurs among patients suffering losses of 600 c.e. or more. Subdivision of the material by color, in this and in other tabulations, by steps of 50 c.e. and 100 c.e., did not alter the picture.

It thus appears that normal multiparas, spontaneously delivered under stable conditions regarding trauma and infection exposure, experience a distinctly increased risk of febrility following excessive bleeding, regardless of their hemoglobin status at term.

There were 32 patients who lost 600 c.e. or more of blood, only 23 of whom had hemoglobin determinations within four weeks prior to term. This number is too small, and the bleeding range too great (up to 1,500 c.e.) for subdivision according to hemoglobin levels, color, and place of confinement. Discarding these 23 cases, there remain 978 case records of normal multiparas of known late gestational blood status with spontaneous onset and termination of labor at term, experiencing blood losses of less than 600 c.e. These were analyzed as regards fever incidence in relation to both blood loss at delivery and the late prenatal hemoglobin level.

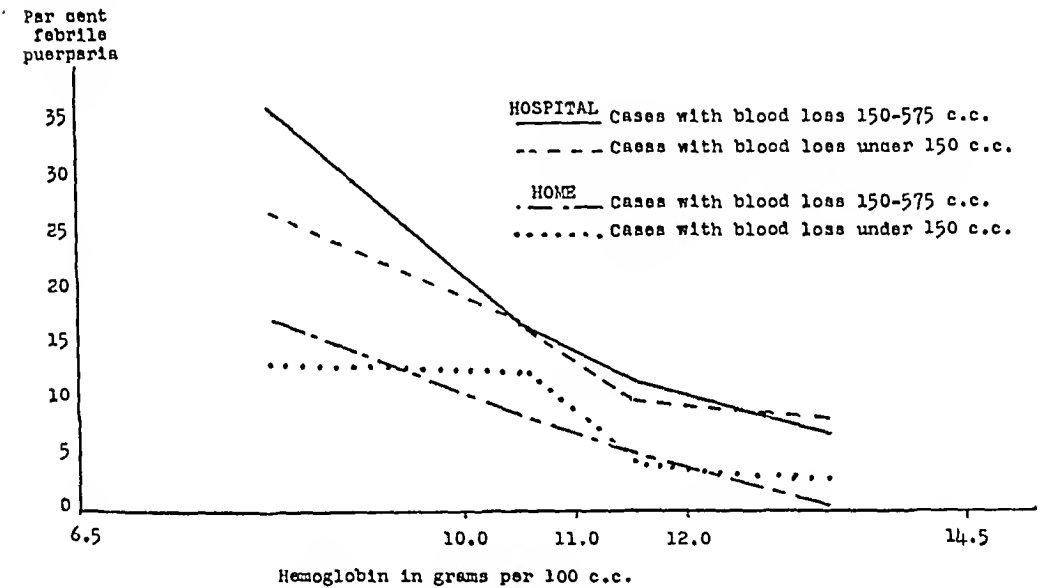


Fig. 3.—Relation of late prenatal hemoglobin level to puerperal febrility for cases in similar ranges of delivery blood loss from 467 hospital and 511 home deliveries. (Summary tabulation not shown.)

TABLE V. PUERPERAL FEBRILITY RATES FOR VARYING AMOUNTS OF BLOOD LOSS AT DELIVERY

From records of 2,015 normal multiparas with spontaneous term deliveries, showing number of cases and percentage febrile, by place of confinement, and amount of blood loss, estimated or measured*

BLOOD LOSS TO NEAREST 25 C.C.	HOSPITAL (MEASURED ONLY)*		HOSPITAL (MEASURED AND ESTIMATED)		HOME (ESTIMATED)*		TOTAL (MEASURED AND ESTIMATED)	
	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%
0-125	149	8.1	527	8.0	569	4.7	1,096	6.3
150-275	133	9.0	294	9.9	332	4.5	626	7.0
300-425	74	8.1	116	6.9	92	8.7	208	7.7
450-575	25	0.0	31	3.2	22	4.5	53	3.8
600 and over	15	26.7	20	30.0	12	16.7	32	25.0
Totals	396	8.6	988	8.7	1,027	5.2	2,015	6.9

*Only occasional blood loss measured in home delivery. Measured in 40 per cent of hospital cases; shown in first column for comparison.

TABLE VI. PUERPERAL FEBRILITY RATES ACCORDING TO PRENATAL HEMOGLOBIN LEVEL AND EXTENT OF BLEEDING AT DELIVERY

From records of 978 normal multiparas, spontaneous term deliveries, with blood losses under 600 c.c., showing number of cases and percentage febrile, by color, place of confinement, amount of bleeding, and hemoglobin level in last month of gestation

HEMOGLOBIN GRAMS PER 100 C.C.	WHITE										NEGRO									
	BLOOD LOSS TO NEAREST 25 C.C.										BLOOD LOSS TO NEAREST 25 C.C.									
	0-125					150-575					0-125					150-575				
	NO. OF CASES	FEBRILE %	NO. OF CASES	FEBRILE %	TOTALS	NO. OF CASES	FEBRILE %	NO. OF CASES	FEBRILE %	TOTALS	NO. OF CASES	FEBRILE %	NO. OF CASES	FEBRILE %	TOTALS	NO. OF CASES	FEBRILE %	NO. OF CASES	FEBRILE %	TOTALS
<i>Hospital Cases</i>																				
6.5- 9.9	23	13.0	21	19.0	44	15.9		33	15.1	23	30.4		56	21.4						
10.0-10.9	32	9.4	39	5.1	71	7.0		40	12.5	40	10.0		80	11.2						
11.0-11.9	28	3.6	32	6.2	60	5.0		24	4.2	20	10.0		44	6.8						
12.0-14.5	40	2.5	47	2.1	87	2.3		11	9.1	14	0.0		25	4.0						
Totals	123	6.5	139	6.5	262	6.5		108	11.1	97	13.4		205	12.2						
<i>Home Cases</i>																				
6.5- 9.9	8	12.5	7	14.3	15	13.3		68	10.3	45	13.3		113	11.5						
10.0-10.9	21	9.5	24	0.0	45	4.4		59	6.8	58	5.2		117	6.0						
11.0-11.9	21	4.8	25	0.0	46	2.2		51	2.0	39	2.6		90	2.2						
12.0-14.5	24	0.0	28	0.0	52	0.0		20	5.0	13	0.0		33	3.0						
Totals	74	5.4	84	1.2	158	3.2		198	6.6	155	6.5		353	6.5						

The blood loss value of 150 c.c. is approximately the median for the group as a whole. The median hemoglobin value is 11.5 Gm. for white patients and 10.5 Gm. for negroes. The 978 were divided according to blood loss ranges above and below the median, and hemoglobin ranges embracing the two median values and the extremes in each direction. The numbers and corresponding rates are given in Table VI. Fig. 3 shows febrility by changing hemoglobin levels for patients with great and small blood losses, in hospital and at home.

Within like hemoglobin ranges, comparisons of fever rates by the extent of bleeding, in this and in other tabulations, fail to disclose a distinct pattern. The blood loss determinations if not entirely accurate are certainly adequate for establishing the broad limits used. Within the limits shown, and consistently throughout other subdivisions of blood loss, the inverse relationship of febrile puerperiums to late gestational hemoglobin is constant and distinct. This suggests that under comparable conditions of trauma and infection exposure, and in the absence of serious hemorrhage, the incidence of febrile morbidity is more closely related to the blood content at term than to the amount of bleeding incident to delivery.

Morbidity comparisons by color, for varying hemoglobin levels, may be made from Tables III and VI. Total negro rates, for each place of confinement, bear a two to one ratio to corresponding total white rates. This ratio exists in the total cases studied, and has long been observed in the general experience of the Service. Compared within similar hemoglobin ranges, however, the negro and white rates are more nearly equal, the ratios centering about 1.3 or 1.4 to 1. In Table I the negro and white cases have obviously different distributions into hemoglobin levels. Taken together, these findings suggest that the lower hemoglobin values prevailing among negroes account, in part, for the much greater incidence of febrile puerperiums which they experience.

SUMMARY

1. Records of 2,018 consecutive multiparas, with normal term pregnancies and spontaneous home or hospital deliveries, are reviewed. Conditions of trauma, infection exposure and handling were reasonably homogeneous for the group.

2. Hemoglobin determinations, within four weeks ante partum, were available in 1,001 cases. A marked, almost uninterrupted, decline of the incidence of febrility, with increasing values of hemoglobin, is reflected throughout various tabulations by color and place of confinement.

3. The rates of febrility based upon all febrile reactions, including "one-day fever," show a similar arrangement.

4. This relationship persists through and above a hemoglobin range ordinarily considered satisfactory.

5. Delivery blood loss was measured or estimated in 2,015 cases. For losses of 600 c.c. or more, fever rates were two to ten times the rates for lesser amounts of bleeding. Blood loss within "normal" ranges was not demonstrably related to febrility.

6. Patients with blood losses of less than 600 c.c., when subdivided according to prenatal hemoglobin levels and amounts of blood loss, present evidence that puerperal morbidity is related to the blood status at term, more closely than to bleeding at delivery, short of serious hemorrhage.

7. Racial comparisons of hemoglobin distribution, total fever rates, and rates within corresponding hemoglobin ranges, give evidence that the low prenatal blood values prevailing among negroes on this service are an important factor contributing to their much greater incidence of puerperal morbidity.

8. The findings indicate that an acid hematin test, during the last month of pregnancy, is a useful index of potential resistance to infection. They serve to emphasize the importance of hemoglobin determinations at intervals during pregnancy. Commonly encountered values between 10.0 and 12.0 Gm., whether "normal" or not, seem to express a status distinctly less satisfactory than higher levels. With due respect to the conservation of blood at delivery, the blood content with which a woman reaches term seems deserving of equally energetic attention.

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It has been repeatedly reported that the symptoms of an allergy in women tend to become aggravated before and during menstruation. Asthmatic symptoms, however, usually improve with the onset of the flow. This might be due to (1) increased general irritability, (2) possibility that patient is sensitive to progestin or theelin, or (3) that premenstrually the blood contains an increased amount or again abnormally low amount of certain hormones.

Blood estrogen determinations on 79 allergic patients showed a premenstrual relative estrogen deficiency in 63.3 per cent, compared with 4.7 per cent in 42 non-allergic women.

Administration of large doses of theelin and lipolutin premenstrually was of benefit only to a limited number of patients who had symptoms exclusively before and during menstruation.

HUGO EHRENFEST.

ABORTION IN RABBITS FED A VITAMIN K DEFICIENT DIET*

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EARLY in the modern investigations of hypoprothrombinemia, Brinkhous, Smith, and Warner showed that the blood of the newborn infant contains only a fraction of the prothrombin present in the blood of the adult. This observation has been repeatedly confirmed by all who have used the titration method of Warner, Brinkhous, and Smith for the determination of prothrombin (Javert and Moore, and Hellman and Shettles). Tests by the technique of Quick do not show this neonatal deficiency (Quick and Grossman). Both procedures reveal a fall in the level of prothrombin during the neonatal period, starting from six to forty-eight hours after birth and continuing for several days (Owen, Hoffman, Ziffren, and Smith).

In the original series of Brinkhous, Smith, and Warner, one infant with clinical hemorrhagic disease of the newborn infant had an extremely low level of prothrombin. Shortly after the time when vitamin K became available for clinical trial Waddell, Guerri, Bray, and Kelley found that the administration of vitamin K to two newborn infants with an abnormally high prothrombin time and clotting time gave a prompt and striking reduction of these two laboratory measurements of the bleeding tendency. They suggested that vitamin K should be a valuable therapeutic agent in hemorrhagic disease of the newborn infant. These findings were readily confirmed by many investigators, and it was further shown that the same elevation of the prothrombin of the infant was secured when the vitamin was given to the mother before delivery (Shettles, Delfs, and Hellman; Hellman, Moore, and Shettles). Of equal clinical importance was the observation by the above and other investigators (Waddell and Guerri, and Kugelmass) that the bleeding in clinical hemorrhagic disease of the newborn infant ceased on the administration of vitamin K.

From these investigations it may be concluded in broad terms that all newborn infants have a relative deficiency of prothrombin; that when this deficiency is excessive the parenchymatous bleeding of hemorrhagic disease of the newborn infant appears; and that the administration of vitamin K to the mother before delivery or to the infant after birth corrects the deficiency and prevents or stops the bleeding. It is possible that

*This investigation was aided by a grant from the John and Mary R. Markle Foundation.

more precise study will reveal the role of other contributing or accessory etiologic factors, such as birth trauma, disease of the liver of the infant, and toxemia in the mother (Javert).

In the summer of 1938 as the above facts were beginning to unfold, it occurred to us that the production of hemorrhagic disease of the newborn in an experimental animal would give the investigator a more convenient and exact method by which to study this disease. Reports in two publications gave encouragement that the project was feasible. First, Moore, Brodie, and Hope showed that the newborn pups of rats fed a diet deficient in certain elements of the B complex died soon after birth, and that there were hemorrhages in the viscera and in the subcutaneous tissues. Second, in the calves of cows with sweet clover disease, there was abundant evidence of hemorrhage and at times it was sufficiently severe to lead to death (Roderick and Schalk).

The original purpose of the experiment, the production, and study of experimental hemorrhagic disease of the newborn was a complete failure, but the unexpected finding of abortion in all animals on a vitamin K deficient diet justifies a full report. The rabbit was selected as the experimental animal because of the ease of breeding, the relatively short period of gestation and the size of the animal. The latter point was important, as the withdrawal of considerable amounts of blood was necessary to follow the level of the plasma prothrombin. The artificial diet was based on the principles followed by Goldblatt and Moritz in their study of avitaminosis D in the rabbit. There was a vitamin-free source of protein, carbohydrate, and fat. Minerals, vitamins, and other materials were added to these basic constituents. The diets used in the two experiments to be reported were different and are designated R-2 and R-3.

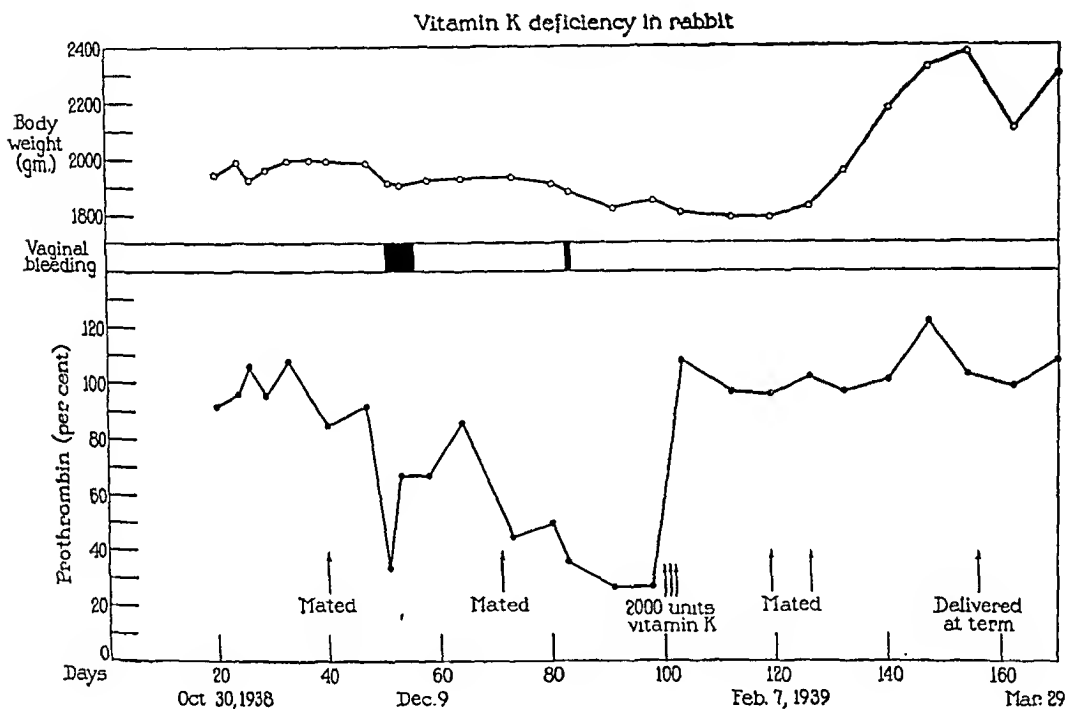
DIET R-2 (FIRST EXPERIMENT)

Dried egg white	150
Wheat starch	375
Cottonseed oil	112.5
Salts (McCollum 165)	32.5
Yeast (extracted with acetone in Soxhlet for 8 hours)	32.5
Agar	32.5
Cod-liver oil	15
Alfalfa powder (extracted with acetone in Soxhlet for 24 hours)	750
Water	to proper consistency
Germinated wheat oil	1 drop per day
Cevitamic acid	5 mg. per day

Diet R-3, used in the second experiment, was the same except that casein extracted with acetone for eight hours in a Soxhlet was substituted for the dried egg white. All of the materials except the wheat oil and cevitamic acid were thoroughly mixed, made into a dough with water and dried as pellets. Most of the rabbits ate the diet, but a few had to be

fed for the first few days at the beginning of an experiment. The ascorbic acid and wheat germ oil were fed with a pipette in the quantities indicated. The agar served to prevent diarrhea and the alfalfa was a source of roughage. The control animals received the same diet except that the alfalfa was not extracted. At intervals, the plasma prothrombin was determined according to the technique of Warner, Brinkhous, and Smith.

The first experiments on 6 rabbits were conducted at Cornell University Medical College during 1938 and 1939, and the second group of four animals were studied at the Washington University School of Medicine in 1939 and 1940.



animals went through a second normal pregnancy. One experimental animal was mated a third time and at the onset of the vaginal bleeding on the eleventh day, a hysterectomy was performed in order to secure material for histologic studies. One animal died two days after the onset of bleeding of the second abortion. The remaining two experimental animals, which had been on the diet for one hundred days and aborted twice, were given 2,000 units of klotogen on each of three days and then bred on the one hundred and tenth day. The artificial diet was maintained, except that these animals now received the same mixture as the control animals. Both matings resulted in a normal pregnancy with 5 to 6 living pups.

The plasma prothrombin in the experimental animals fell progressively, with a maximal decrease of 79 units or to 75 per cent of the original values. When abortion occurred, the determinations were always less than 35 per cent of normal. Following the administration of klotogen, the prothrombin returned to normal within three days. The results in one animal are shown graphically in Fig. 1.

SECOND EXPERIMENT

In the summer of 1939, synthetic pure chemical substances with great biologic activity as vitamin K became available; and it was decided that the experiments should be repeated under better conditions of control.

Four Dutch rabbits were placed in wire bottom cages and fed the deficient diet designated R-3. An oily solution of 2-methyl-1,4-naphthoquinone was given in doses of 1 mg. in 0.2 c.c. of oil every other day. After from twenty to thirty days all animals were mated and a normal pregnancy resulted. The young were destroyed and the mothers were continued on the deficient diet without the added 2-methyl-1,4-naphthoquinone. After forty days of this regime the animals were mated. On the ninth day all aborted. Placentas were recovered from two animals. After two to three weeks, a second pregnancy during the feeding of the deficient diet was initiated. All animals aborted on the eighth to the eleventh day, and two animals died in the succeeding week on the third and seventh day after the appearance of vaginal bleeding. Both were emaciated. The remaining two animals were given the same doses of 2-methyl-1,4-naphthoquinone as in the pre-experimental period and mated on the twentieth and twenty-fifth day. A normal term pregnancy with live pups resulted in both.

Prothrombin determinations in this experiment were confined to two values during each of the three periods, pre-experimental, experimental, and postexperimental, to establish that there was a normal value in the first and last and a low value in the second.

PATHOLOGIC CHANGES IN THE PLACENTAS

As noted above, placentas from 3 abortions in the first experiment and 2 in the second were recovered, fixed and sectioned. A composite description is as follows:

Sections of the placenta appeared to be normal except for the decidual plate. In all the sections there was hemorrhage in the decidual plate. These areas of hemorrhage were both recent and old. In the recent areas, the red cells appeared normal; in the older areas they had become decolorized; and in the still older areas the blood clot had been replaced

by laminated fibrin. There was not enough decidua present in any of the sections to determine the exact site of origin of these hemorrhages. However, this lesion was microscopically identical to that seen in retroplacental hemorrhage associated with human abortion.

DISCUSSION

Although the experiments comprehend only a relatively few animals the constancy of the results in all animals on two different occasions clearly indicates a relation between vitamin K deficiency and abortion in rabbits during the late first and early second trimester. The known effect of vitamin K deficiency in the production of hemorrhage and the finding of retroplacental hemorrhage in the rabbits point to the same conclusion. The fact that hemorrhage occurred at this point and not at other points in the body and that the plasma prothrombin had not fallen to the so-called critical levels of 10 to 25 per cent, suggests that the placenta is unusually susceptible to deprivation of vitamin K.

The adequate supply of vitamins A, B, C, D, and E in both experiments would appear to eliminate them as a cause of the pathologic change. Great care was taken to see that all animals received vitamin E, because of the known relation to reproduction and fetal resorption. The absence of abortions in the postexperimental period of the second experiments gives direct evidence that the deficiency was due to vitamin K.

Whether or not vitamin K deficiency is the cause of abortion in women cannot be ascertained from the facts at hand. The report of Javert is suggestive. In one patient with retroplacental hemorrhage, the cord blood contained only 13 per cent of normal prothrombin, but the mother's prothrombin was normal. Any further conclusions must await a comprehensive study of prothrombin before, during, and after abortion in a large number of women.

CONCLUSIONS

Vitamin K deficiency and hypoprothrombinemia in pregnant rabbits result in abortion at the end of the first trimester of gestation. The application of this observation to the study and treatment of abortion in women must await further study.

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THE ANOVULATORY FACTOR IN STERILITY*

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THE increasing use of endometrial biopsies in recent years has focused considerable attention upon the anovulatory factor in sterility. Recently we have taken endometrial biopsies from a number of sterility patients in the immediate premenstrual interval to determine the presence, or absence, of ovulation. Initial examination of 42 cases in this manner showed normal ovulation in 62 per cent (26 patients), and absence of ovulation in 38 per cent (16 patients). Critical examination of the ordinary clinical data on these anovulatory patients failed to show any findings, other than endometrial biopsy, to suggest an absence of ovulation. The incidence of anovulatory menstruation in sterility patients has been recorded by the following observers: 33 per cent, Mazer and Israel;⁶ 29 per cent, Siegler;¹¹ 25 per cent, Jeffcoate;⁴ 36 per cent, Kotz and Parker;⁵ and 48 per cent, Novak.⁷ Rock, Bartlett, and Matson⁹ found in a series of 392 sterile patients that 9 per cent had an occasional anovulatory period, and that 4 per cent were habitually anovulatory. This emphasizes the need for more than one endometrial biopsy before judging a patient to be persistently anovulatory.

Our report deals with the effects of pregnant mare serum injections into anovulatory sterile patients who presented no gross pathologic findings. It was possible to give pregnant mare serum injections to 8 of the 16 anovulatory sterile patients in this series. Repeated endometrial biopsies were used before and after the injections to give controlled evidence of the therapeutic results. These showed evidence of ovulation after pregnant mare serum injections in 7 of 8 proved anovulatory patients. Only one pregnancy resulted in this anovulatory group, and this one terminated in an early miscarriage. It is unfair to blame this relative absence of pregnancy entirely upon the gonadotropic agent,

*Presented as a Scientific Exhibit at Michigan State Medical Society, Grand Rapids, September, 1941.

since all of the other important sterility factors were controllable in only 3 of these 8 anovulatory patients. The essential clinical facts are listed in summarized form by the following case reports.

CASE 1.—Patient, aged 22 years, married two and one-half years, had an early spontaneous miscarriage six months after marriage. No contraception and no pregnancy since that time. Menses were regular twenty-eight to thirty-day interval, and of six-days' duration. Endometrial biopsy, taken in premenstrual stage, showed proliferative type with no ovulation. Mare serum was given in dosage of 400 i. u. on the twelfth day, and 600 i. u. on the fourteenth day. Endometrial biopsy on the twenty-second day showed evidence of ovulation.

CASE 2.—Patient, aged 28 years, married four and one-half years, had used no contraception and had had no pregnancy. Menses were regular twenty-eight-day type. Duration of flow was normally seven days, but for last year periods had lasted ten to fourteen days in profuse amount. Premenstrual endometrium showed no evidence of ovulation. Mare serum was given: 400 i. u. on tenth day, and repeated on the twelfth day. Endometrial biopsy on the nineteenth day of the cycle showed no evidence of ovulation. This treatment was repeated for a total of three months without producing ovulation. The menorrhagia disappeared during the course of the above treatment.

CASE 3.—Patient, aged 30 years, married four years, had used no contraception and no pregnancy had occurred. Menses were always irregular with interval varying between three and twelve weeks. Premenstrual endometrium showed dilated tubular acini with no ovulation. Mare serum was used as 400 i. u. on the tenth day and 800 i. u. on the twelfth day. Biopsy one week later showed no ovulation. Treatment with mare serum was repeated during the next month on the tenth and twelfth day of the cycle, 800 i. u. on each day. Premenstrual biopsy again showed no ovulation. This same dosage was used during the next month and premenstrual endometrial examination showed ovulation to have occurred this time.

CASE 4.—Patient, aged 30 years, married five years, had used no contraception for last three years and had had no pregnancy. Menses regular with twenty-six to twenty-eight-day interval. Endometrial biopsy on twenty-second day of the cycle showed no ovulation. Mare serum was given: 400 i. u. on the twelfth day and 800 i. u. on the fourteenth day. Biopsy one week later showed the presence of ovulation. Further sterility factors discovered were closed tubes and non-motile sperms.

CASE 5.—Patient, aged 25 years, married 4 years, had used no contraception for three years and had had no pregnancy. Menses were irregular every four to eight weeks. Six premenstrual endometrial biopsies between 1938 and 1940 showed no ovulation. Mare serum was used: 400 i. u. on the eleventh day and 800 i. u. on the thirteenth day. Biopsy one week later showed a secretory endometrium (Fig. 1). Mare serum therapy was continued until pregnancy resulted after two months of treatment. Miscarriage occurred after three months' amenorrhea.

CASE 6.—Patient, aged 29 years, had used no contraception and had had no pregnancy during three years of marriage. Premenstrual biopsy showed no ovulation. Mare serum injections were given: 400 i. u. each



Fig. 1.

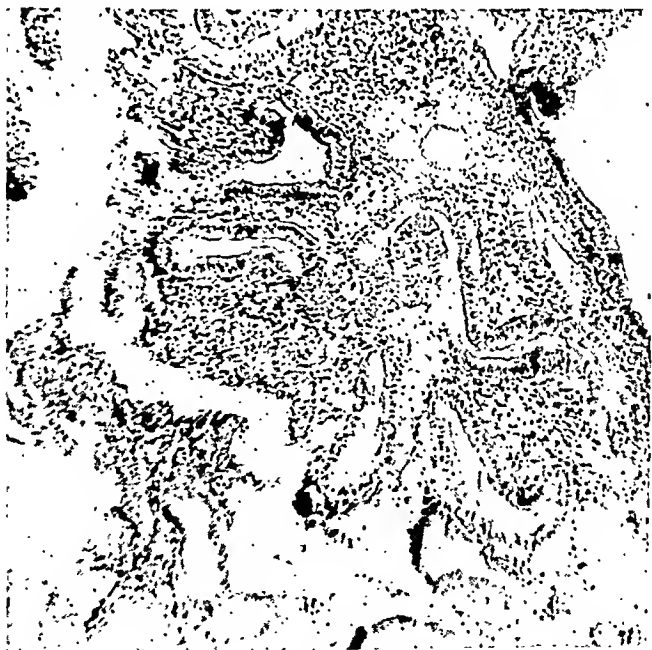


Fig. 2.

on the eleventh and fourteenth day. No ovulation was produced during the first month of this treatment, but evidence of ovulation was found following the second course of injections (Fig. 2).

CASE 7.—Patient, aged 39 years, had 2 pregnancies soon after the first marriage, fifteen years previously. There had been no pregnancy since second marriage, 2 years ago. Menses were regular and normal. Premenstrual endometrial biopsy showed no evidence of ovulation. Mare serum used: 400 i. u. each on the ninth and twelfth day. Biopsy of endometrium one week later showed ovulation to have occurred following these injections.

CASE 8.—Patient, aged 35 years, had been married ten years but had had no pregnancy. Menses were usually of twenty-eight-day interval, but occasionally missed one period. Several biopsies taken in the premenstrual interval showed no ovulation. Mare serum was used in dosage of 400 i. u. each on the twelfth and fourteenth days. Biopsy one week later showed evidence of ovulation.

DISCUSSION

A critical analysis of these case reports brings up some interesting considerations. Novak⁸ expresses the almost universally accepted opinion that endometrial biopsy is the most reliable indicator of ovulation. However, Hamblen² states that ovulation may be present in an occasional case, evidenced by the presence of sodium pregnanediol glycuronide in the urine, without the usual biopsy findings due to a refractory condition of the endometrium. While further work will settle this question, the preponderance of opinion at this time favors the view that endometrial biopsy gives correct information regarding ovulation. The first endometrial change after ovulation consists in a ranging into line of the nuclei of the gland cells. This process has been described by Hisaw,³ Sturgis and Meigs,¹² Kotz and Parker,⁵ Roek,¹⁰ Novak,⁸ Campbell, Lendrum, and Sevringhaus,¹ and others. Under the estrogenic influence of the proliferative phase the nuclei of the gland cells are situated at irregular levels with respect to the bases of the cells. With the advent of the lutein influence immediately after ovulation, it is commonly believed that this change is reflected in the endometrium by a ranging into line of these nuclei at a level somewhat near the centers of the cells. The clear spaces below this regular line of nuclei consist of glycogen granules, demonstrable by Best's carmine stain. Some observers (Novak,⁸ Roek¹⁰) have noted a tendency for the gland cell nuclei to range into line and undergo mobilization in castrate patients treated with estrogenic substances. Roek has stated further that the nuclear changes in such cases are patchy and lack the uniformity seen in cases where ovulation has occurred. Our experience has included some 600 endometrial biopsies from patients with a variety of gynecologic conditions. Complete clinical diagnosis and follow-up were possible since this material came from private patients entirely. Correlation of biopsy and clinical findings leads us to support the view that endometrial biopsy is a reliable indicator of ovulation, and that the earliest microscopic sign of ovulation consists in a ranging into line and mobilization of the nuclei in the endometrial gland cells.

SUMMARY

Pregnant mare serum injections were followed by ovulation in 7 of 8 anovulatory patients, evidenced by endometrial biopsies taken before and after the gonadotropic treatment.

The authors wish to acknowledge their thanks to the Schering Corporation and to the Upjohn Company for the mare serum hormone used in these studies. The injection dosage is expressed in international units on the basis that 10 Cartland-Nelson units (gonadogen, Upjohn Co.) are equivalent to 200 international units (aneron, Schering Corporation).

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MALIGNANCY OF THE VULVA

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MALIGNANCY of the vulva is a comparatively rare disease.¹ At the Free Hospital for Women between January, 1890, and January, 1941, 66 cases have been seen. In the same interval there were 1,668 cases of carcinoma of the cervix, 475 of the body of the uterus, 179 of the ovary, and 562 of the breast. During this period there have been approximately 32,511 hospital admissions, making the incidence of carcinoma of the vulva 0.2 per cent in this gynecologic clinic.

Ages.—The youngest patient with malignancy of the vulva was 37 years of age, the oldest 85. All but 11 patients were over 50 years of age, the average being 60.5 years. This average age is five years higher than that of 100 women on whom superficial vulvotomies were performed for leucoplakia and kraurosis of the vulva,² lesions considered as precursors to carcinoma of the vulva.³

Location.—Of the 66 cases, the malignancy arose from the labia in 39 instances, usually on a leucoplakic base, but in one instance the seat of origin was a hidradenoma. The growth was sufficiently extensive to involve both sides of the vulva in 15 cases. In 24 cases it was unilateral, being present 12 times equally on each side. Malignancy was located

about the urethra in 9 cases. Since it is impossible in most instances to determine conclusively whether the cancer started in the urethra and spread outward, or began in the vulva and grew into the urethra, these 9 cases have been included as vulva cancer. In 10 patients the clitoris was the chief area involved. Bartholin's gland was included in the tumor on 4 occasions although an adenocarcinoma was present in only 1 of them. In 2 cases the disease commenced on the perineum at the fourchette. Venereal warts were associated with the disease in one of the perineal and one of the labial cases. Two of the patients had had vulvectomy elsewhere, and on admission to this Hospital had groin involvement, although the original lesion was absent.

Symptoms and Duration.—Multiple complaints were common. The most frequent one, however, was that of a growth in the vulva region. This occurred 44 times; on 28 occasions it was described as a "lump" and on 16 as an "ulcer." Irritation was the complaint 32 times and was mentioned as itching in 21 instances and burning and smarting in 11 others. Bleeding was associated in 18 cases although it was the chief complaint in only 5. Ten patients were bothered by dysuria, but in only 1 case was it the presenting symptom. Leucorrhea was the only complaint on 1 occasion but was mentioned in 4 others.

The duration of symptoms before the patient sought medical advice is appalling. Only 4 patients presented themselves in less than one month from the time of onset and only 1 of these had an early lesion. She was a patient who was being followed in this clinic after treatment for a carcinoma of the cervix. Forty patients presented themselves in less than a year from the beginning of symptoms, but of these only 27 were seen in less than six months and 15 in less than three. Nineteen patients had had difficulties for more than a year and 14 of these for more than two years. In 7 the history was indefinite. Thus only one-third had reported in less than six months while another third had had symptoms for more than a year. Itching and smarting of the vulva as well as persistent tumors and ulcers should be stressed as danger signals in cancer of the vulva. Too often, patients feel that itching is something of which they should be ashamed and hesitate to be examined. Moreover, local applications are hopefully indulged in over too long a period.

Pathology.—In this series there were found 1 fibrosarcoma, 1 hemangiosarcoma, and 1 lymphoblastoma of the vulva.* The remainder of the cases were carcinoma, a pathologic diagnosis having been established in all but 5 instances. Of the latter, 2 were moribund on entering the hospital, 3 had no biopsies, but the diagnosis was clinically unmistakable since they died of the disease, 2 within seven months and 1 within three years.

Of the 58 patients in whom cancer was diagnosed microscopically, 56 had epidermoid carcinoma and 2 adenocarcinoma. Either leucoplakia or kraurosis or both were found microscopically in conjunction with the cancer in 38, or 54.5 per cent. Both leucoplakia and kraurosis were present in 25 cases; the former alone in 9, and the latter alone in 2.

*Lymphoblastoma of the vulva is very rare.⁴ This case has been mentioned in Graves, *Gynecology*, Edition IV, 1928, and at that time was believed to be the only case reported in the literature. The slide was examined by Drs. Frank B. Mallory, James Ewing, and S. B. Wolbach. Taussig, however, in 1937, reported a lymphosarcoma of the clitoris.⁵

Our patient when first seen was 43 years old. She had several tumors in the vicinity of the clitoris, the largest measuring 10 by 7.5 by 8 cm. A complete vulvectomy was performed in 1927. A short time later she received x-ray therapy in another city. In 1941 she was enjoying perfect health.

An attempt to grade the cases according to the degree of malignancy was made. This was based largely on the number of mitoses and the tendency to form epithelial pearls. However, it was most unsatisfactory. Except for the general appearance of invasiveness which was influenced by the duration of the disease, there was no marked variation. Metastases appeared in the groins regardless of the degree of malignancy. There was no apparent prognostic significance, the extent of the disease when first seen and the general condition or age of the patient being far more important considerations.

Treatment and Results.—End results are presented on 54 cases which were seen prior to January, 1937, including 7 patients who had been operated upon at other hospitals. This allows for the conventional five-year follow-up. There was a five-year salvage of 15, or 27.7 per cent. For the 47 consecutive cases which had not received previous operative treatment at other hospitals, the salvage was 29.7 per cent. All patients lost were counted dead and all those who had died of any cause whatsoever were considered to have died of cancer.

As may be seen in Table I, many forms of treatment were employed in these 54 cases. The extent of the disease and the condition of the patient were the deciding factors.

TABLE I. FIVE-YEAR SURVIVALS

TREATMENT	NO. OF CASES	SUR- VIVALS	LOST	DEAD	% OF SUR- VIVALS
None	4	0	1	3	0
Radium alone	6	0	0	6	0
Radium plus bilateral groin dis- section	1	0	0	1	0
Radium plus partial vulvectomy	3	1	0	2	33.3
Partial vulvectomy	5	0	4	1	0
Complete vulvectomy	14	5	1	8	35.6
Complete vulvectomy plus unilat- eral groin dissection	3	0	0	3	0
Complete vulvectomy plus bilateral groin dissection	9	5	2	2	55.5
Amputation of clitoris plus radi- um	1	0	1	0	0
Amputation of clitoris	1	0	1	0	0
Excision of urethra plus partial vulvectomy	1	1	0	0	100.0
Excision of tumor plus unilateral groin dissection	3	1	0	2	33.3
Excision of tumor plus bilateral groin dissection	3	2	0	1	66.6
Total	54	15	9	30	27.7

Four patients were not operated upon and all died. Of these, three were moribund on admission and the fourth refused treatment.

Radium was used as part of the initial treatment of 10 patients. On 6 of them it was the only therapy and on the 4 others it was used in conjunction with operation. The disease was advanced in all cases. There was only one survivor and this was a surgical case. The lives of 4 others were perhaps prolonged by the use of radium, since they lived from two to three years.

Partial vulvectomy or local excision was performed 11 times, 4 being in conjunction with radium. Of these there were 2, or 18.1 per cent, five-year survivors.

Complete vulvectomy alone was performed 14 times. Five patients, or 35.6 per cent, were considered cured.

Of 9 cases in which a bilateral groin dissection in addition to a complete vulvectomy was done 5, or 55.6 per cent, lived for five years. Four patients had the vulva and the groins operated upon in 1 stage and 5 in 2 stages with an interval of approximately one month between. Metastases were discovered in the groins in 5 cases. One of the 5, or 20 per cent, survived for five years. Of the cases in which no glandular involvement was found, 3, or 75 per cent, were known to be living and the fourth was thought by relatives to be alive, but could not be traced. She is counted as dead.

In 3 instances the local area was removed and the groin on one side dissected. One, or 33.3 per cent, survived.

In 3 others the local area including the growth was removed without doing a complete vulvectomy, but a bilateral groin dissection was performed as well. Two, or 66.6 per cent, survived.

Although extravagant conclusions cannot be made from a small number of cases, it would appear that groin dissections are important. In most instances a wide vulvectomy plus a bilateral groin dissection (i.e., the Basset operation) should be done, but often the disease is too advanced or the patients are in too poor condition. Many of them are elderly. If the procedure is carried out in two stages, however, it is not particularly shocking. This method tends to prevent hurry and allows for a more complete groin dissection. Moreover, if the wounds become septic postoperatively, there is not such a large gaping area to granulate. In removing the vulva, the use of the diathermy knife is helpful in reducing the amount of blood loss.

Operative Mortality.—Of the 66 patients, 4 were untreated and 7 received radiation alone. Of the 55 patients subjected to surgery in one form or another, 3 died postoperatively, a mortality rate of 5.4 per cent. Two patients died of a pulmonary embolism on the sixth and fifteenth days, respectively. Both deaths followed a vulvectomy. One died on the operating table, a bilateral groin dissection and an excision of one labium having been completed.

Secondary Operations.—Of the 54 patients seen prior to 1937, 5 had further treatment for recurrent disease, other than radiation alone; one had a local recurrence excised two years after her first operation here and thirteen years after the original operation for carcinoma of the vulva at another hospital. She was well three years after the last operation. Another patient had a local excision of the disease plus radium. Three patients had groin dissections at a late date, 2 of them having radium as well. All except the first patient are dead. To be of value, groin dissections must be done as near the time of the vulvectomy as possible, certainly within a month.

Gland Involvement.—In 19 patients who subsequently had an exploration of the groins, a definite preoperative statement was made as to whether metastasis would be found. In 9 the nodes were expected to be malignant and found to be negative in 5. In 10 that were thought to be negative preoperatively, 3 were found to be positive. Thus a correct

clinical diagnosis was made in only a little over 50 per cent. This further substantiates the importance of doing groin dissections.

Radiation.—Of the 66 patients, 21 have been treated with radium. In 6 it was the only form of therapy, since they were advanced cases, and 3 of them had been operated upon elsewhere first. In 8, it was used in conjunction with surgery and to 7 others it was administered for recurrent disease. Of the 21 cases, 4 received more than one application. The total dosage varied between 200 and 4,800 mg. hours, the usual dose being 1,500 to 1,600. There was only one 5-year survivor, and this patient had a wide local excision of the growth as well. In 8 patients, or more than one-third, it was followed by intense pain or sloughing. The larger the dose, the greater was the likelihood that pain would occur, but 1,600 mg. hours in one case and 2,000 in another were enough to cause pain. Except for 5 cases in which the radium was directed to the groins for metastatic disease, it was applied exclusively to the vulva. Thus on the whole radium has been unsatisfactory.

X-radiation was used on 18 cases, 6 times in conjunction with radium. Five times it was directed at the groins only, once at the groin and the vulva, and the remainder at the vulva alone. It was used in conjunction with operation in all but 3 cases; in one it was the only form of therapy, but with the other two radium was used as well. When the groins were radiated, no untoward effects were noted. When the vulva was treated, the burning and pain was similar to that which followed the use of radium in the same region. Its effectiveness is hard to estimate, since comparable cases with and without x-radiation were few. The dosage used varied between 800 and 3,200 r., but approximately 1,600 r. was the usual dose. It seems unwise to use it routinely on the vulva because of the pain that often accompanies it; but on the groins, it does little harm and may be of value.

CONCLUSIONS

1. Malignancy of the vulva is an uncommon disease occurring in 0.2 per cent of the patients at the Free Hospital for Women.
2. It is a disease primarily of women past the age of 50, but may occur in the relatively young.
3. In the majority of cases it is associated with leucoplakia and kranrosis of the vulva. Chronic Bartholinitis, or venereal warts, may be predisposing factors.
4. Epidermoid carcinoma is the usual pathologic picture. Adenocarcinoma or sarcoma is occasionally the type of malignancy. Classification of the degree of malignancy does not seem very helpful from a prognostic point of view.
5. Knowledge of the disease should be more widely disseminated, as the interval between the onset of symptoms and the time of entry into the hospital is too long.
6. For all patients entering this hospital, the five-year salvage is 27.7 per cent. If the patients previously operated upon at other hospitals for the disease are excluded, the total salvage is 29.7 per cent. The operative mortality is 5.4 per cent.

7. Although many forms of therapy have been resorted to, the treatment of choice is a radical vulvectomy plus a bilateral groin dissection. This is dependent on the extent of the disease and the general condition of the patient when first seen. When this is done the prognosis for five-year survival becomes 55.5 per cent.

8. Radiation to the vulva should be used only as a last resort. Either radium or x-ray causes marked discomfort in about one-third of the patients.

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330 DARTMOUTH STREET

MESODERMAL MIXED TUMORS OF THE BODY OF THE UTERUS

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MESODERMAL mixed tumors of the uterus and vagina are extremely rare and highly malignant neoplasms. Since their gross appearance, age incidence, and manner of attachment, when they arise in the body of the uterus, differ so strikingly from similar tumors of the cervix uteri and vagina, it was deemed expedient to confine this study to mesodermal mixed tumors of the body of the uterus.

Weber¹⁶ reported the first case in the cervix uteri in 1867 and Anderson-Edmonnson (quoted by Kehrer⁷) described the first case in the body of the uterus in 1870. The term mesodermal mixed tumor was proposed by Kehrer⁷ and supported by R. Meyer.^{12a} Pfannenstiel¹⁵ employed the term "traubiges Sarkom" or botryoid sarcoma, as it is known in this country, because of the grapelike character of the tumor when it had its origin from the cervix or vagina. This term has been discarded because a botryoid appearance is not a constant characteristic of these tumors, especially when they arise in the body of the uterus.

In a recent publication¹⁰ I collaborated with R. J. Lebowich in a critical analysis of the literature on mesodermal mixed tumors of the body of the uterus. In this study 12 genuine cases were collected, following the pathologic criteria of L  wen,⁹ and an additional case was reported. Since this study 2 papers have been published dealing with mesodermal mixed tumors of the body of the uterus. Although the case of Glass and Goldsmith⁴ presented clinical and pathologic characteristics of a mesodermal mixed tumor, it is unacceptable. The bulk of the tumor consisted of smooth muscle, cartilage, and mucoid tissue, but no true embryonal myoblasts or cross-striated muscle tissue were demonstrated.

Three cases were described by Liebow and¹ Tennant,¹¹ but only one of their cases contained striated embryonic muscle tissue, in addition to other heterotopic mesodermal elements. This brings the number of acceptable reported cases to 14.

CASE REPORT

M. G., a 55-year-old, Russian born, white housewife was admitted into the Beth Israel Hospital on Feb. 16, 1941, complaining of vaginal bleeding of three months' duration. The family history was irrelevant. The patient had suffered with "piles" for many years. About 7 years ago she was treated for dysuria and frequency of urination. She has had 2 children, the last childbirth occurring twenty-eight years previously. An uneventful menopause occurred three years ago.

For the past three months the patient had noticed intermittent vaginal bleeding. This had not been progressive in character. There had been no vaginal discharge in the intervals between bleeding episodes. A history of abdominal pain, urinary or rectal disturbances was not elicited.

A short, soft, systolic murmur was audible in the region of the cardiac apex. The systolic blood pressure was 142 mm. and the diastolic 78 mm. The lungs were clear to percussion and auscultation. Upon deep abdominal palpation a mass could be felt in the midline just above the symphysis pubis.

Vaginal examination revealed a uterus enlarged to the size of a three months' gestation, symmetrical and freely movable. Protruding from the external os was a polypoid mass of tissue; when the mass was grasped with a tenaculum, the tissue tore easily, leaving a raw, ragged, freely bleeding surface.

Laboratory Data.—Urine: specific gravity, 1.022; acid; albumen, 2-plus; sugar, negative; 1 to 2 white blood count per high power field. Hematologic: Hg (Sahli), 98 per cent; red blood count, 4,000,000; white blood count, 11,400. Differential smear: polymorphonuclear leucocytes, 65 per cent; lymphocytes, 25 per cent; monocytes, 10 per cent. Complement fixation test for syphilis, negative. Phenolsulphonephthalein dye test, total dye excretion of 60 per cent in two hours.

On Feb. 16, 1941, under spinal anesthesia, a vaginal hysterectomy was performed. The postoperative course was uneventful. The patient was discharged from the hospital on Feb. 26, 1941.

From March 10, 1941, to April 22, 1941, she received a total of 30 x-ray treatments. Each treatment was 156 r. without back-scattering. They were given through 4 pelvic portals, 2 anteriorly and 2 posteriorly. The following factors were used: 180 KV, 4MA, 0.5 mm. Cu., 1.0 mm. Al.

Periodic examination revealed no local recurrences, intra-abdominal masses, ascites, or any evidence of metastases. The patient has been symptom free and has not lost weight.

Microscopic examination of the biopsy specimen showed scattered throughout all the sections large areas of edema, inflammation, and necrosis. For the most part the tissue was composed of small, ovoid to spindle-shaped cells with similarly shaped nuclei. Many of these cells appeared to have cytoplasmic processes, which did not fuse with each other to form a network. This has probably been brought about by the edema, which has dissected the tissue apart. In some areas large cells with eosinophilic cytoplasm were found. The nuclei of these cells were bizarrely shaped and in some instances the cells were multinucleated. They strongly suggested cells of muscle origin. In one field a small area

of necrotic cartilaginous tissue was seen. Mitoses of all elements were numerous. Striated muscle cells could not be demonstrated.

The specimen removed at operation consisted of a soft, club-shaped uterus, 12.5 cm. long. The tubal angles were 5.5 cm. apart and the anteroposterior diameter was 4.5 cm. The external os and cervical canal were widened and coated with iodine. Upon opening the cervical canal anteriorly, an irregularly shaped, soft mass bulged. The lower portion of this mass hung down to within 1.5 cm. of the external os and looked like a blood clot (Fig. 1). The upper portion of the mass was ovoid, with the long axis in the axis of the uterus. The length of the mass, except for the lowermost portion which seemed to consist of a blood clot, was 7 cm.; the transverse diameter was 3 cm. and the anteroposterior



Fig. 1.—Midsagittal section of uterus, after fixation, showing polypoid mass attached to the midportion of the uterine wall by a short pedicle. Above the tumor mass, note the thickness of the endometrium, which was the seat of an adenocarcinoma.

diameter was 4 cm. The mass was soft, highly edematous, partly pale grayish yellow and partly bloody. It was attached to the left side of the uterine wall in its lower half and was also attached to the left half of the posterior uterine wall, including the left tubal angle. Below the attachments, in the region of the external os, there were shallow, yellowish gray protrusions, which seemed to be part of the tumor. A smaller and firmer protrusion was situated in the anterior wall, in the region of the internal os slightly to the right of the midline; to the naked eye this protrusion had no connection with the tumor mass. The endometrium, outside the tumor, was thick, pale, and edematous. It contained a thin-walled cyst, the size of a pea.

Midsagittal section following fixation showed the uterine cavity above the tumor straight, narrow, and appearing to be pushed forward. The

thickness of the submucous muscular layer posteriorly reached 1.7 cm.; the thickness of the entire wall was 3 cm. and that of the endometrium 6 mm. At the upper end of the attachment of the tumor, a thin, gray, slightly curved, membranous layer was seen. This layer appeared to be continuous with the endometrium. The large protrusion on the cut surface was composed of a number of distinctly outlined, grayish masses whose gross appearance was not unlike that of myomas. These masses were separated from each other by narrow and broader bands of partly opaque, but mostly glassy grayish and purplish grayish tissue. The lower part of the tumor was diffusely glassy and yellow. The endometrium above the tumor appeared pale gray and opaque. There was a small area of endometrium-like tissue below the tumor in the region of the internal os. (This corresponded to the swelling described before fixation.) The lowermost portion of the tumor, which appeared bloody from the outside, was also bloody on the cut surface.

Representative blocks of tissue were fixed in formalin and stained with hematoxylin-eosin, van Gieson, Best's glycogen stain, Mayer's mucicarmine, iron-hematoxylin, sudan IV, polychrome methylene blue, and azocarmine.

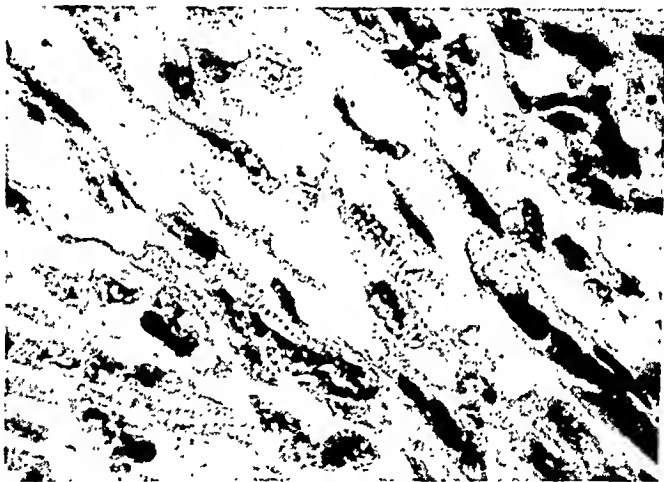


Fig. 2.—Cross-striated muscle cells in a mucoid stroma.

The picture was partly similar to that seen in the biopsy. Necrosis, edema, inflammation, fibrosis, and hemorrhage were unusually extensive in sections taken from the mass which protruded into the uterine cavity. The essential matrix of the tumor consisted of a mucoid tissue containing spindle-shaped or triangular cells with long, fine, protoplasmic strands which appeared to form a network. These areas, however, did not stain red with mucicarmine. In addition a variety of heterologous elements and structures were encountered, both in the tumor mass and uterine wall.

Areas of spindle-cell sarcoma were scattered throughout all sections and were most numerous within the substance of the tumor. In many sections long eosinophilic cells were seen, some of them with longitudinal fibrils. These cells contained centrally placed nuclei, in the vicinity of which definite cross-striations were encountered (Fig. 2). The cells were no wider than the nucleus, but the cytoplasm swelled to accommodate it. Many of the cross-striated cells were short and blunt.

Occasional small islands of cartilage (Fig. 3) were present in sections taken from the tumor. These cartilaginous islands were encircled by a dense collar of small, round cells and spindle cells. Metachromasia could not be demonstrated in such areas when stained with polychrome methylene blue.

Adjacent to some of the areas containing striated embryonal muscle cells were clusters of large vacuolated cells, which somewhat resembled adipose tissue. A negative reaction was obtained when such areas were stained with sudan IV.

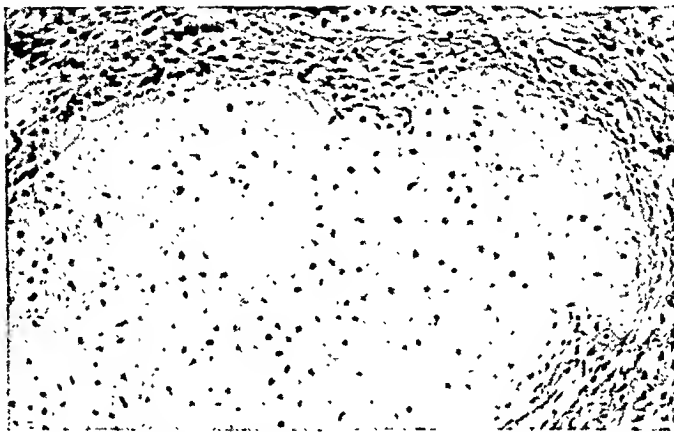


Fig. 3.—Part of an island of embryonal cartilage. An area of spindle-cell sarcoma overlies the cartilaginous tissue.



Fig. 4.—An area of adenocarcinoma with squamous metaplasia.

A portion of the endometrium adjacent to the tumor was the seat of the usual type of adenocarcinoma, which in places infiltrated the muscularis for some distance. Areas of adenocarcinoma and sarcoma did not appear to fuse, although the endometrium in some places was seen to be supplanted by sarcomatous areas. Squamous metaplasia was observed in adenocarcinomatous glands (Fig. 4). In some places where the endometrium was not invaded by carcinoma, there was metaplasia to squamous epithelium, which showed keratinization.

A fairly extensive internal adenomyosis was present. In some areas the adenomyotic structures were associated with squamous metaplasia,

and in other areas squamous epithelial plaques were embedded within the uterine musculature, without accompanying endometrial glands.

True lymphatic tissue was not encountered, but sparsely scattered lymphoid foci were seen. Their cells resembled normal adult lymphocytes.

Large, bizarrely shaped, multinucleated cells were occasionally seen in areas containing cross-striated muscle tissue. These cells were not encountered in the endometrium or in areas of apparently uninvolved uterine musculature.

The tumor was richly vascularized with capillaries and thin-walled veins. No tumor thrombi were seen.

DISCUSSION

Histogenesis.—There has been much speculation with regard to the histogenesis of these tumors, and many theories, all unsatisfactory, have been advanced.

The hypothesis, proposed by Pfannenstiel,¹⁵ that the numerous heterologous elements have their origin in the connective tissue of the endometrium and later undergo a process of metaplasia has had little support. A transformation of nonstriated into striated muscle cells has never been demonstrated. Wilms¹⁷ has advanced the theory that the tumors have their origin in primitive mesodermal tissue which has been carried downward during descent of the Wolffian duct. Although the complex nature of the tumor would favor such a concept, the absence of striated muscle in the Wolffian body, together with the development of the tumor outside the course of the Wolffian duct, controvert Wilms' contention.

An origin from cell rests of the Müllerian ducts, following their fusion to form the uterus and upper vagina, seems more plausible, especially since these tumors have been observed to develop at the base of the bladder. Such tumors have never been observed to occur in the broad ligament, and this would contradict the Müllerian duct theory. According to R. Meyer,^{12b} embryonal cell rests are not uncommon in the uterus and vagina. These cell rests are epithelial and do not, therefore, lend support to the Müllerian duct theory. This hypothesis has won the support of Mönckeberg,¹³ Kehrer,⁷ and Lahm.⁸

Differential Diagnosis.—The histologic diagnosis of mesodermal mixed tumors rests upon the demonstration of striated embryonic muscle tissue in combination with one or more heterologous elements like mucoid tissue, cartilage, etc. This has been emphasized by Lävén.⁹ The presence of embryonal myoblasts per se does not warrant the diagnosis of mesodermal mixed tumor. A variety of tumors may cause confusion, and in the differential diagnosis, a fibromyoma undergoing ossification or cartilaginous changes, myosarcoma, rhabdomyoma, teratoma, carcinosarcoma, chondroma, myxochondrosarcoma, and the myoblastoma of Abrikossoff¹ must be excluded. If a large number of representative sections are examined and the pathologic criteria of Lävén are followed, there should be no difficulty in diagnosis.

In addition to the variety of elements and structures contained in our case, osteoid tissue^{2, 10} and fat¹⁰ have been reported. True bone, bone marrow, lymphatic tissue, and nerve tissue have not been described. A superimposed adenocarcinoma, as occurred in our case, is distinctly uncommon, although carcinomatous changes were present in the cases of Lävén⁹ and Nicholson.¹⁴

Recurrence and Metastases.—Local recurrences have been an almost constant feature in all cases, and distant metastases involving the pleuras, lungs, liver, and pelvic and abdominal peritoneum are frequent. Local extension into the parametria, bladder, and rectum has not been described. Cervical extension is uncommon; it has only been observed in 2 instances.^{5, 6} Apparently lymphatic extension does not play a dominant role, as it does in carcinoma of the body of the uterus. Metastases to the lumbar lymph nodes, which are so frequently involved in carcinoma of the body of the uterus, have only been encountered in one case.¹⁰

Comparison With Cervical and Vaginal Tumors.—The tumors are encountered in the cervix and vagina two or three times more frequently than in the body of the uterus. Vaginal tumors occur during childhood, cervical tumors during the active sexual decades, and corporal tumors during and after the menopause. The cervical and vaginal growths differ from the corporal tumors only in their gross appearance, being arborescent in character. In the body of the uterus the neoplasm is almost always polypoid and frequently is attached to the uterine wall by a distinct pedicle.

Clinical Features.—Symptomatology and physical findings do not differ essentially from the picture presented by carcinoma of the uterus. Since there is no tendency toward infiltration of the parametria and other pelvic viscera, the growth usually remains freely movable, even after it has grown to considerable proportions. It is not unusual for the tumor to attempt to deliver itself through the cervical canal, as occurred in our case and in the cases of von Franqué³ and Halter.⁵

Panhysterectomy followed by adequate irradiation should be the treatment of choice. There have been no cases on record in which the patients were treated with radiation alone. Inasmuch as the bulk of the tumor is composed of embryonal elements, postoperative irradiation is worthy of a trial.

The prognosis is poor. Recurrence in about one year after operative removal has almost been the rule.

SUMMARY

A case of mesodermal mixed tumor of the body of the uterus plus a superimposed adenocarcinoma has been described. Fourteen similar cases have been collected from the literature. The histogenesis is obscure; the Müllerian duct theory seems the most acceptable, but far from satisfactory. The diagnostic importance of striated embryonic muscle tissue has been emphasized. Total hysterectomy and removal of the tubes and ovaries, followed by adequate irradiation, appears to be the treatment of choice. There have been no five-year cures of verified cases reported.

I wish to thank Dr. Henry C. Falk for permission to publish this case and Dr. Alfred Plaut for his helpful criticisms.

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INTRATESTICULAR HEMORRHAGE: A BIRTH TRAUMA

WITH A REPORT OF EIGHT CASES

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THE occurrence of intratesticular hemorrhage during birth in breech presentation is well recognized. It is not generally known, however, that such hemorrhage occurs as a birth trauma when the head is the presenting part. Furthermore, it is not realized that such hemorrhage occurs rather frequently and that it may be quite extensive. An incidental observation of such an instance led me routinely to make gross and microscopic examination of the testicles of newborn infants at necropsy. In slightly over a year, among 21 male infants who died when less than one week old, 7 cases were encountered. An additional one was observed by Dr. Newbill.

REPORT OF CASES

CASE 1.—A negro boy was born on Oct. 2, 1940, at 4:32 P.M. of an eclamptic mother at the estimated seventh month of pregnancy. The presentation was vertex and the position L.O.A. The child was blue, responded poorly to resuscitation, and died at 8 A.M. the next day.

At necropsy (A40-1112) the child was 42 cm. long, weighed 1,660 Gm., and had atelectasis of the lungs. There were multiple microscopic hemorrhages in the lungs, liver, kidneys, and in the glomus chorioideum of each lateral ventricle. The testicles were contained in the scrotum and were of usual size. The cut surfaces were dark red. Microscopic examination disclosed massive extravasation of blood beneath the tunica albuginea and in the tissues between the primitive seminiferous tubules (Fig. 1).

CASE 2.—A white boy was born on Dec. 13, 1940, at 3:36 A.M. at the estimated ninth month of pregnancy. The duration of labor was about

twelve hours, the presentation was vertex and the position L.O.A. The child was dead at birth.

At necropsy (A40-1349) the child was 44 cm. long, weighed 1,700 Gm., and had fetal atelectasis of the lungs and a "horseshoe" kidney. There were petechiae over the pericardial and pleural surfaces. The scrotum was enlarged and edematous. The testicles were descended and were dark red on their cut surfaces. Microscopic examination disclosed massive extravasation of blood in the tissues between the primitive seminiferous tubules.



Fig. 1.

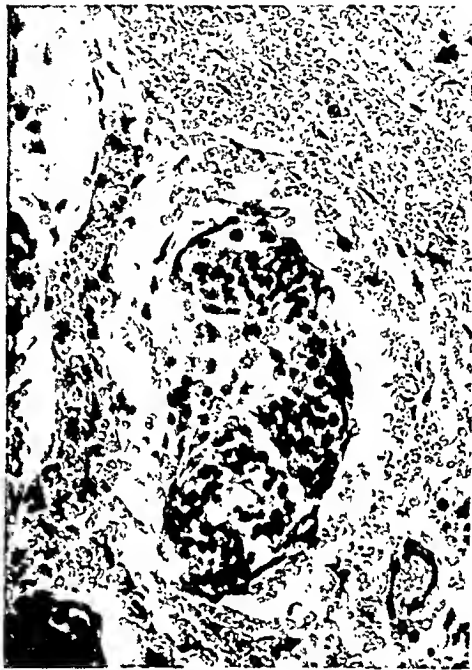


Fig. 2.

Fig. 1.—Massive extravasation of blood between the primitive seminiferous tubules of the testicle of a negro boy who died less than sixteen hours after birth (A40-1112).

Fig. 2.—Extravasation of blood between the primitive seminiferous tubules of the testicle of a white boy who died less than two days after birth (A41-739).

CASE 3.—A negro boy was born on Feb. 18, 1941, at 4:30 A.M. at the estimated seventh month of pregnancy. The presentation was vertex and the position L.O.A. The heart sounds and primary respirations were poor. The child died on February 20 at 1:30 A.M.

At necropsy (A41-198) the child was 39 cm. long, weighed 1,300 Gm., had massive hemorrhage into the lateral cerebral ventricles from the terminal veins, and had atelectasis of the lungs. The scrotum was edematous. Both testicles were descended. The right testicle was proportionate and appeared dark red. Microscopic examination disclosed extensive areas of extravasation of blood beneath the tunica albuginea and hemorrhage into the stroma between the primitive seminiferous tubules, and between the tubules of the epididymis.

CASE 4.—A white boy was born on Aug. 9, 1941, at 8:51 A.M. at the estimated ninth month of pregnancy. The mother was a primipara;

her Wassermann reaction was negative. The duration of labor was about twenty-eight hours; the presentation was vertex; and the position R.O.A. Low forceps was attempted and was followed by spontaneous delivery. The child did not do well and died on August 11 at 6:15 A.M.

At necropsy (A41-739) the child was 50 cm. long, weighed 3,160 Gm., and had bilateral tears in the tentorium cerebelli, fetal atelectasis of the lungs, and uric acid infarcts in the kidneys. There were microscopie hemorrhages in the lungs and glomus chorioideum. There was slight edema of the serotum. The testicles were descended and of usual size. Microscopic examination disclosed focal areas of extravasation of blood in the stroma between the primitive seminiferous tubules, in the hilus, and beneath the tunica albuginea (Fig. 2).

CASE 5.—A negro boy was born on July 31, 1941, at 9:10 A.M. at about term. The duration of labor was sixteen hours, and the position L.O.A. The primary respirations were poor. The child was cyanotic and many petechiae were noted over the body. Vitamin K was given intramuscularly and intravenously, and 10 c.c. of blood were injected into the gluteal region. Each injection was followed by bleeding. The child died at 3 P.M. the same day.

At necropsy (A41-748) (by Dr. Hugh P. Newbill) the child was 52 cm. long, weighed 3,105 Gm., had fetal atelectasis of the lungs with focal pneumonia, and numerous petechiae in the skin, conjunctivae, pleura, and pericardium. There were hemorrhages also in the leptomeninges and dura mater. The testicles were of usual size and dark red on their cut surfaces. Microscopic examination disclosed massive extravasation of blood beneath the tunica albuginea and in the stroma between the primitive seminiferous tubules.

CASE 6.—A white boy was born on Aug. 14, 1941, at 7:10 A.M. at the estimated ninth month of pregnancy. The mother was a primipara. The duration of labor was fifty-six hours. The presentation was vertex and the delivery was with high forceps. The heart sounds were not heard at birth, and there were no primary respirations.

At necropsy (A41-751) the child was 54 cm. long, weighed 4,200 Gm. and had fetal atelectasis of the lungs and microscopie hemorrhages in the glomus chorioideum. The serotum was edematous, and there was a right hydrocele containing about 3 c.c. of light yellow fluid. The testicles were of usual size and dark red. Microscopic examination disclosed massive extravasation of blood in the septa between the lobules and in the interstitial tissue between the primitive seminiferous tubules and beneath the tunica albuginea (Fig. 3).

CASE 7.—A negro boy was born on Aug. 31, 1941, at 11:55 A.M. at the estimated ninth month of pregnancy. The mother was a primipara, and her Wassermann reaction was positive. The duration of labor was four hours. The presentation was vertex and the position R.O.A. The delivery was spontaneous. The child cried weakly and remained cyanotic. It was placed in an oxygen tent and died at 2:10 P.M.

At necropsy (A41-835) the child was 45 cm. long, weighed 2,330 Gm., had hemorrhage into the right lateral ventricle of the brain from the vena terminalis and had bilateral focal pneumonia. The microscopie

changes in the liver, lungs, spleen, and pancreas were compatible with syphilis. The testicles were symmetrical and dark red. Microscopic examination disclosed diffuse areas of extravasation of blood beneath

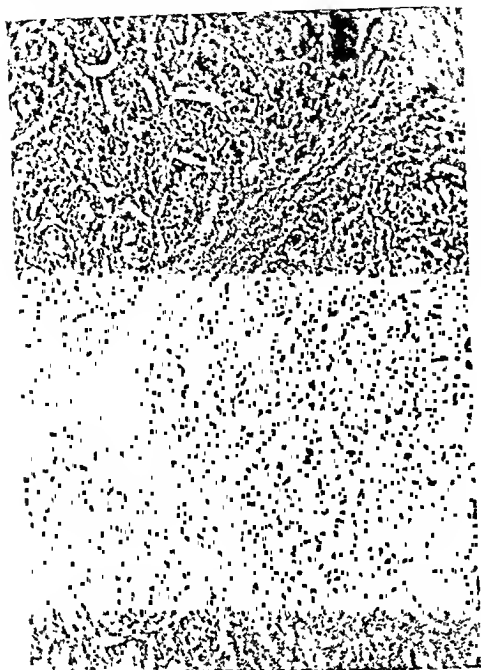


Fig. 3.

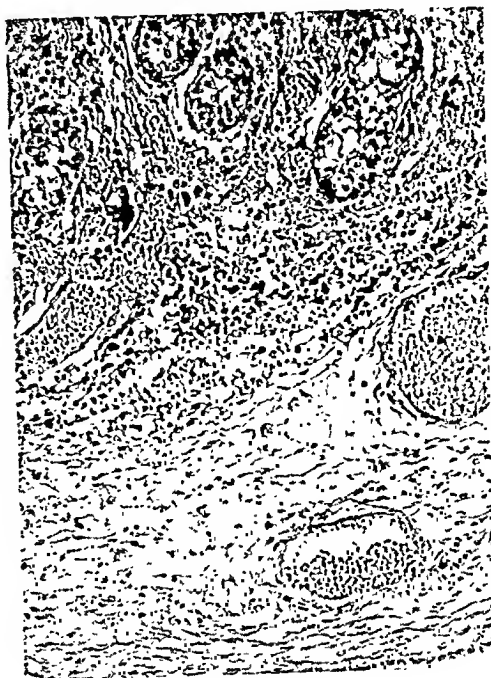


Fig. 4.

Fig. 3.—Extravasation of blood in the septa between the lobules and in the stroma between the primitive seminiferous tubules of the testicle of a white boy who died during delivery (A41-751).

Fig. 4.—Extravasation of blood beneath the tunica albuginea and in the stroma between the primitive seminiferous tubules of a negro boy who died two hours after birth (A41-835).

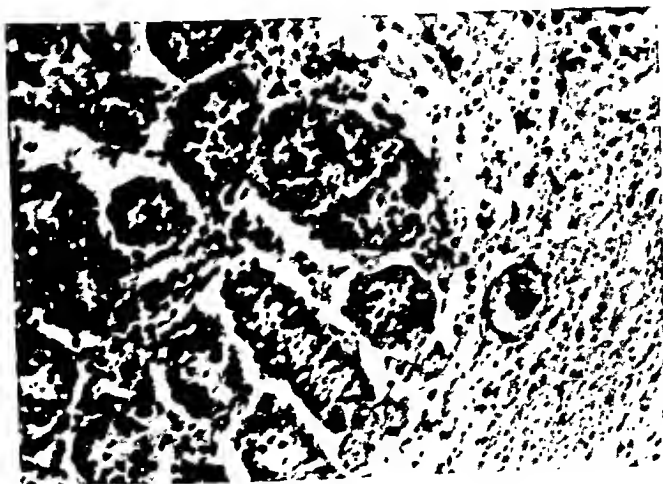


Fig. 5.—Extravasation of blood along the inner surface of the tunica albuginea of the testicle of a negro boy who died less than four days after birth (A41-1032).

the tunica albuginea and in the connective tissue between the primitive seminiferous tubules. Blood-forming islands were seen scattered in the stroma (Fig. 4).

CASE 8.—A negro boy was born in Oct. 23, 1941, at 11:24 A.M. at the estimated ninth month of pregnancy. The duration of labor was fifteen hours, the presentation vertex, and the position L.O.A. The delivery was spontaneous and the child was in good condition at birth. It developed a temperature of 102° F. on October 25 and died on October 27 at 4 A.M.

At necropsy (A41-1032) the child was 50 cm. long, weighed 3,330 Gm. and had suppurative leptomeningitis and bilateral focal pneumonia. Both testicles were dark red, and their capsules were smooth. Microscopic examination of transverse sections of one and of longitudinal sections of the other testis and epididymis disclosed extravasation of blood along the inner surface of the tunica albuginea and in the stroma between the primitive seminiferous tubules (Fig. 5).

COMMENT

In his study on visceral hemorrhages in stillborn children, Spencer¹ (1890) observed intratesticular hemorrhage in 15 of 78 male children. In 8 cases the presentation was breech or footling, and in one case it was vertex, faec (?), conduplicatio corpore, and unknown. The 3 remaining cases were described as being delivered by forceps.

Simmonds² (1910), in a paper presented before the Biologic Section of the Hamburg Medical Society, was the first to emphasize the frequent occurrence of intratesticular hemorrhage, both in breech presentation and also in head presentation. He regarded asphyxia as the cause of hemorrhage in both instances. In the discussion, Plate explained that after the head had passed through the birth canal the contraction of the vulva forces the blood toward the caudal end of the child. Hemorrhage occurs because the testicles are situated outside the peritoneal cavity, and there is no contrapressure to protect them.

This explanation of Plate perhaps is correct, first because asphyxial hemorrhages elsewhere are not necessarily accompanied by hemorrhage in the testicles, and second because intratesticular hemorrhage may occur in cases in which there is no hemorrhage elsewhere.

SUMMARY

Attention is called to the frequent occurrence of intratesticular hemorrhage as an injury sustained during birth in cases where the head is the presenting part.

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GESTATION FOURTEEN YEARS AFTER RADIUM INDUCED AMENORRHEA*

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THE report of this case is of interest for it presents several problems worthy of consideration because of the widespread use of radiation for various gynecologic conditions.

The possibility of conception occurring following intrauterine radium treatment of pelvic pathologic conditions has been accepted and is an established fact. However, in reviewing the literature on this subject, one finds that gestation after fourteen years' amenorrhea following the intrauterine application of radium is a rare occurrence.

In the treatment of functional female disorders, especially where subsequent pregnancies are desired, the use of radiation has not yet been universally approved. There are many instances reported of the birth of abnormal children following irradiation.⁴ It is also noted that there is a tendency toward abortion in the first pregnancies following irradiation, while later pregnancies may terminate in normal offsprings.¹ There is therefore that danger in temporary radium sterilization, and some authorities advocate that permanent rather than temporary sterilization be performed.

Pregnancies have been reported after radium therapy for various pathologic conditions, such as cancer of the body of the uterus, of the cervix, fibroids, *et cetera*.

I. Kaplan² reports a case in which carcinoma of the cervix complicating pregnancy was given x-ray therapy and was followed by the birth of a normal child.

C. Karg¹ discusses the history of two women who conceived after restoration of menstruation following intrauterine radiotherapy. Both patients aborted.

P. Burger³ reviews a series of cases collected by Flaseamp. In 117 patients who had been irradiated with roentgen rays, there were 133 gestations, and among 46 women treated with radium, 54 pregnancies occurred. He states, that it is well known that infants born after irradiation which was given during pregnancy are frequently deformed, the nervous system being particularly involved and defective. In cases where the irradiation was carried out in the pregestational period, the children born after such treatment are nearly always normal. However some authors maintain that such babies may also be born with malformations.

D. P. Murphy⁴ reviews over 283 pregnancies in women subjected to pelvic irradiation with the conclusion that "there is yet no definite indication that ovarian irradiation prior to fertilization has any detrimental influence upon the health or development of any subsequent children: that, irradiation of pregnant women is a procedure extremely dangerous to the health of the offspring (61.3 per cent being defective) and should not be undertaken unless the existing pregnancies are to be terminated artificially prior to the period of viability of the child." Of 230 pregnancies occurring in women who received preconception pelvic irradiation, 50 aborted (21.7 per cent). Of the 180 children born at term 27

*Presented at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

(15 per cent) presented some disturbances of health or defect in development.

Ovaries vary greatly in their sensitivity to radium therapy. Most of the full-term deliveries take place within a three-year period after radiation. The less the amount of radiation the more frequent the conception and possible full-term delivery. The chances for conception are least after an 1,800 mg. hours of radiation.

CASE REPORT

Patient S. B., white, 47 years of age, acutely ill and anemic in appearance, was admitted to the Brooklyn Jewish Hospital on May 22, 1941, with a history of backaches for six months and amenorrhea for fourteen years following radium therapy. For the past week patient experienced severe lower abdominal cramps associated with staining and profuse bleeding on the last day. This was accompanied by fainting spells. She had been married for twenty-seven years, and was a para ii, gravida iv, her youngest child being twenty-three years old. Eighteen years previously she was admitted to the Jewish Hospital for an incomplete abortion when a curettage was performed. Fourteen years ago she was treated at the hospital for pernicious vomiting of pregnancy for several days and finally a therapeutic abortion was performed.

Several months later patient was readmitted to the hospital with a history of menorrhagia and metrorrhagia. At this time a dilatation and curettage were performed, and radium inserted for 1,200 mg. hours. The pathologic report of the curettings was that of interstitial endometritis.

Physical Examination.—Head and neck were negative; pupils reacted to light and accommodation; lungs were negative; heart was enlarged, and the sounds were muffled and weak but regular; extremities were negative. The findings at the present admission were: On abdominal examination a mass was palpable, arising from the pelvis and extending halfway to the umbilicus. Pelvic examination revealed profuse vaginal bleeding with blood clots; good parous pelvic floor; a parous cervix which was patulous admitting one finger with which a mass was palpable, suggestive of a submucous fibroid. The uterus was found to be the size of a three months' pregnancy; the fornices were negative. A diagnosis of submucous fibroid was made.

Laboratory Data.—The hemoglobin was 62 per cent; red blood cells, 3.20 million; white blood cells, 10,000; urinalysis, negative; blood pressure, 90/60.

The patient was operated upon on May 22, 1941. A midline infra-umbilical incision was made. The uterus was found to be smooth and enlarged to about a three months' gestation. Both ovaries were found to be sclerotic with the right one larger than the left. Both tubes were found to be normal. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed in the usual manner, the cervical stump being peritonized and hemostasis completed. The abdomen was closed in layers without drainage.

Patient was discharged on the nineteenth day due to a slight wound infection.

Pathologic Report.—Gross Examination: The specimen was a pear-shaped uterus amputated above the cervix with attached tubes and ovaries. Uterus measured 11 by 7 by 4 cm. Its external surface was pink gray, smooth, and glistening. The uterine canal measured 10 cm. in length and was occupied by purple red tissue, clotted blood and a

glistening red membrane. The myometrium measured 1 to 2 cm. in thickness and presented nothing of note. The right Fallopian tube measured 7.5 cm. by 0.4 cm. The fibrated extremity and lumen were patent. The external surface was pink red, smooth, and glistening. The right ovary measured 3.5 by 2 by 1.2 cm. The external surface was pink yellow and gyrated. In the cut surfaces there was a corpus luteum measuring 1.8 cm. in diameter.

The left Fallopian tube measured 6 by 0.4 cm. and was similar to the right.

The left ovary measured 2.5 by 2 by 0.6 cm. and presented nothing of note.

Microscopic Examination: Attached to the endometrial surface was clotted blood in which were seen well-defined chorionic villi lined by preserved Langhans and superciliary cells, as well as poorly defined villi or ghosts of such structure. Syncytial buds were also noted as well as islands of decidual cells. In places there was a dense infiltration by many polymorphonuclear leucocytes. The cellular infiltration was also seen extending into the myometrium. The myometrial bundles were large and spread apart by edematous interstitial connective tissue. Another fragment consisted of extravasated blood with occasional scattered chorionic villi. Two other preparations from the uterus showed similar pictures.

Preparation from the right ovary showed ovarian stroma with a large corpus luteum. The luteum cells were well preserved. The Fallopian tubes showed a narrow lumen, the inner surface of which was thrown into papillary folds covered by cylindrical cells. The connective tissue stalks were delicate. The muscular coat was not remarkable.

Preparations from the left ovary likewise showed ovarian stroma with old and more recent corpora albicantia.

Pathologic diagnosis was a gravid uterus with placental tissue. This was, of course, at variance with our preoperative diagnosis of submucous fibroid, and a postoperative diagnosis of incomplete abortion was made.

CONCLUSION

From the pathologic report of the condition of the ovaries with evidence of follicular activity and recent corpora lutea, we are to deduce that, although no menstruation has occurred, cyclic ovarian function existed. We must, therefore, assume that, due to some change in the hormonal balance, the ovaries had regenerated and become susceptible once more to the constant stimulation of the pituitary gonadotropes. After sufficient regeneration of ovarian function, there is produced an adequate amount of estrogens and progesterone which in conjunction with the activity of some other organs, influence the regeneration and development of the endometrium and uterine activity. This constant stimulation produces a suitable endometrium in time, so that nidation of the ovum and gestation may ensue without the occurrence of any previous cyclic bleeding.

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OVARIAN TUMOR WITH MASCULINIZING SYNDROME

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TRUE masculinizing tumors of the ovary are uncommon and great confusion prevails concerning the pathogenesis, structure, classification, and nomenclature of these neoplasms. Novak¹ classifies those ovarian tumors shown to possess endocrine activity as (1) granulosa cell carcinoma, (2) thecoma, (3) luteoma, (4) arrhenoblastoma, (5) adrenal ovarian tumors, and (6) the so-called struma ovarii or thyroid tumor of the ovary. With the exception of the last two, all are looked on as of dysontogenetic origin arising from abnormalities in the early stages of gonadogenesis.

Reis and Saphir² classify true masculinizing tumors as (1) arrhenoblastoma, said to arise from misplaced testicular structures located within or close to the ovary, (2) disgerminoma, believed to arise from early gonad cells before such cells have been differentiated into either ovarian or testicular structure although occasionally disgerminomas do not produce symptoms of masculinization, and (3) hypernephroma, interrenalism or Grawitz tumor, believed by many to arise from misplaced suprarenal cortical rests within the ovary. Others,³ however, believe that these tumors arise from lutein cells of the ovary and therefore designate them as luteomas.

The evidence presented herewith seems to indicate that the following case falls within this latter category.

REPORT OF CASE

Miss B. V., an unmarried girl of Spanish parentage, aged 23 years, came under observation on Nov. 29, 1938. Except for pneumonia in infancy, her past medical history was unimportant. Family history revealed that her mother died of cancer of the stomach at the age of 30, and her father died of tuberculosis at the age of 30. Her menses began at 14 years and were regular until 1935 when amenorrhea occurred for one year, followed by irregularity. With the onset of amenorrhea there was a coincidental overgrowth of hair, at first on the face and chest, later covering the back, abdomen, and legs. She gained 30 pounds following the beginning of her illness but lost 10 pounds during the past six months. During the past five months she complained of menorrhagia and metrorrhagia.

Physical Examination.—The patient was a short (61 inches) and somewhat obese young woman weighing 131 pounds. The obesity involved the trunk, neck, and face, being much less marked in the extremities. The texture of the skin was coarse, and there were numerous purplish-brown striae along the sides of the abdomen, the hips, and the breasts. Her voice was husky but still feminine. There was pronounced hypertrichosis of the entire body, the hair being heavy, black, coarse, and of definite male distribution with pudendal excess extending above the umbilicus (Fig. 1). Hair had been removed from the face by x-ray treatments given elsewhere six months prior to admission to

the Clinic. The arms and legs were heavily covered as were the dorsal surfaces of the fingers and toes. The eyes were prominent and the face moon shaped.

Vaginal examination showed marked hypertrophy of the clitoris which measured 1 cm. in diameter and $1\frac{1}{2}$ cm. in length. There was a purulent bloody discharge from the vagina. The cervix was firm and irregular, and a small, fatty mass protruded from the external os. The uterus was markedly enlarged and measured about 10 by 14 cm. in diameter. It was hard, smooth, and movable. The adnexa were not palpable.



Fig. 1.

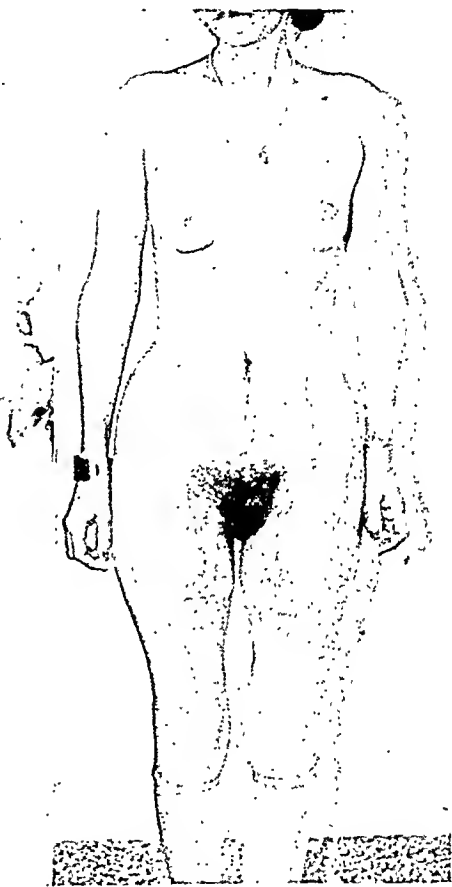


Fig. 2.

Fig. 1.—Prior to removal of the ovarian tumor.

Fig. 2.—One year after removal of the ovarian tumor.

Roentgen examination of the skull, sella turcica and long bones showed no unusual changes other than a slight amount of decalcification of the dorsum sellae.

Laboratory Data.—The urine was negative except for a few pus cells in clumps. The blood count showed 11,500 leucocytes, 4,600,000 erythrocytes, and 71 per cent hemoglobin. The blood Wassermann was negative. Chemical analysis of the blood showed 200 mg. of cholesterol, 10.4 mg. of calcium, 320 mg. of sodium, and 511 mg. of sodium chlorides per 100 c.c. The carbon dioxide content was 56 volume per cent. The dextrose tolerance test showed 91 mg. of sugar per 100 c.c. during fasting, 250

mg. one-half hour after ingestion of 100 Gm. of dextrose, 246 mg. after one hour, and 200 mg. after two hours.

At operation on Feb. 3, 1939, the uterus was found to be symmetrically enlarged to the approximate size of a three months' pregnancy, and contained a small nodule on the anterior aspect. The right ovary was smaller than normal and appeared sclerotic. The left ovary was enlarged to the size of 4 to 5 cm. in its widest diameter. The left ovary and uterus were removed after careful palpation of both renal and adrenal regions had failed to demonstrate any adrenal tumor.

The postoperative course in general was very stormy. Immediately following operation the patient was in a state of surgical shock. Large amounts of adrenal-cortin, together with other measures taken to combat shock, brought about a notable improvement within forty-eight hours. The patient remained in the hospital for three months during which

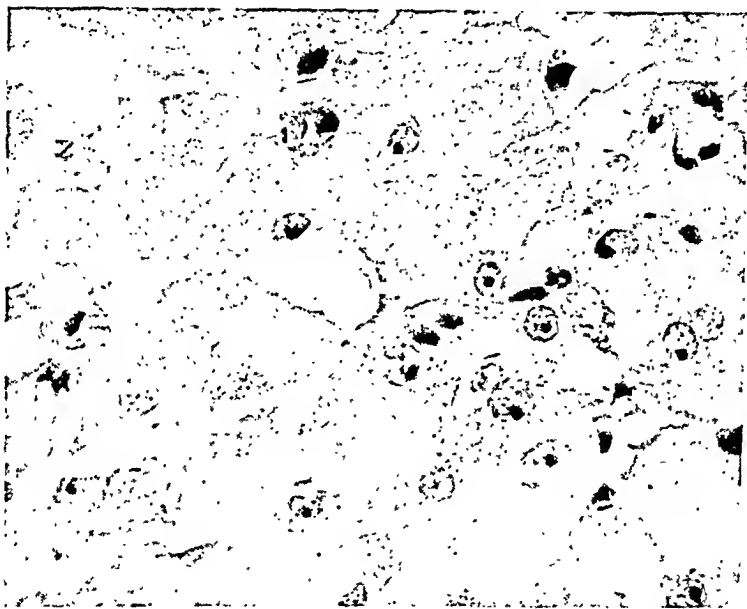


Fig. 3.—Photomicrograph (high power) showing section of the ovarian tumor. Hematoxylin and eosin stain. Note large polyhedral cells, clear cytoplasm, and distinct cellular outlines.

time she frequently manifested emotional and nervous upsets, such as persistent emesis, headaches, and spells of crying. Furuncles appeared frequently in various areas and the surgical wound was slow in healing. After four months, her emotional adjustment and general health were near normal. The hirsutism on the chest and back had markedly decreased, the voice was softer but the size of the clitoris had not diminished. A year later (Fig. 2) the breasts were larger, the figure had become more feminine and the masculine distribution of hair had entirely disappeared. The clitoris had decreased in size.

*Pathologic Report.**—The specimen consisted of an ovary and uterus. The ovary measured 6.5 cm. in diameter, was semifluctuant in consistency, and had a bluish green capsule. Approximately two-thirds of the ovary was composed of a single cyst measuring 4 cm. in diameter and lined by a smooth grayish pink surface. It contained turbid, reddish

*The author is indebted to Dr. Angus Wright and Dr. A. R. Camero for their assistance and advice on the pathologic aspects of this case.

brown, thin fluid. The adjacent portion of the ovary was composed of a firm rim of brownish yellow, cellular tissue, apparently enclosed within the capsule of the ovary. The uterus measured 14 by 9 by 9 cm. in diameter and had a small fibromatous nodule beneath the serosa. The cut surface showed thin, cordlike whorls of fibrous connective tissue within the myometrium.

Histologic examination of the ovary showed that the brownish yellow tissue described before was grossly made up of large cells containing an abundant amount of granular, pink-staining cytoplasm (Fig. 3) with large nuclei and conspicuous nucleoli (Fig. 4). These cells were arranged in irregular strands and many of them contained granular brown pigment within their cytoplasm and some of them exceedingly large nuclei. A number of large spaces within the tumor were lined by cells of the type described. Fat stain showed that the large cells

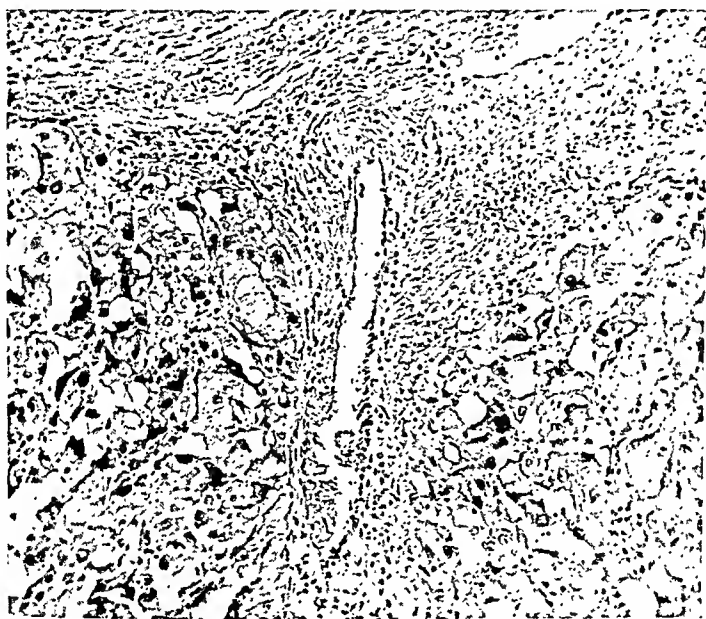


Fig. 4.—Photomicrograph (low power) showing section of the ovarian tumor stained with hematoxylin and eosin. Note the large, polyhedral cells, abundant cytoplasm with large nuclei and conspicuous nucleoli.

contained a few fine granules of fat-staining material in addition to brown pigment which did not stain. Ponceau-Fuchsin stain showed that these cells gave the reaction of virilism as noted in certain cortical adrenal tumors.

DISCUSSION

Kermauner believes that such tumors arise from lutein cells of the ovary. Masson⁴ points out that the luteoma may be recognized by a fine, reticulum network similar to that seen in the corpus luteum and that such reticulum cannot be found in tumors which arise from the suprarenal cortex, but Saphir⁵ counters with the statement that there are hypernephromas in which reticulum is demonstrable. Novak⁶ expresses doubt that the mature functioning lutein cells could be the source of tumor growth. He believes that certain granulosa cell cancers can exhibit a lutein-cell transformation of the constituent cells to such an extent that the tumor might be converted into a lutein-cell tumor. He

and Plate⁷ have individually seen such histologic transformations in parts of tumors which were clearly of the granulosa-cell variety. Schiller⁸ coincides with Novak and is convinced that, with a very few possible exceptions, such tumors are of the adrenal rather than the lutein character. On the other hand, Reis and Saphir are convinced that, anatomically, it is not possible to differentiate between lutein cell blastoma and hypernephroma but that both types of tumor may coexist or develop in the ovary. Hoehloff⁹ called his tumor a hypernephroma of the ovary but Kermauner believed that the tumor might equally have been called a lutein cell blastoma.

When Rottino and McGrath¹⁰ submitted slides of their case to various physicians, E. Novak, R. Meyer, W. Schiller, and D. Symmers expressed the opinion that the growth arose from an adrenal rest. Vines and Broster,¹¹ however, felt that the growth was not of adrenal origin and suggested luteinic origin instead. Saphir, who also studied a slide, believed that it was a true tumor-luteoma or hypernephroid and different from his case. Rottino and McGrath concluded that, aside from size, they could see no difference between their case and that of Saphir's.

Norris¹² is convinced that positive identification of these tumors cannot be made until the hormone is isolated and its physiologic activity demonstrated. He recommends that hormonal studies be made before and after operation to help establish the nature of the disturbance. Schiller points out, however, that the ovaries develop substances of virilizing effect and that testicles produce folliculin. What holds for the physiologic tissue may be found in even greater degree in tumors developing from it. For that reason, he thinks it is not safe to prove the origin of virilizing or masculinizing tumors by their production of substances of sex influencing capacity. He believes that, for the time being, it is much safer to rely on morphologic criteria exclusively for the classification of such tumors.

SUMMARY

The case presented here may be regarded as an instance of the condition under discussion, for clinical masculinility developed in a patient who previously had been completely feminine. Furthermore, the removal of the left ovary was followed by a reversal of symptoms with re-establishment of female habitus. The yellowish-brown tumor of the left ovary was composed histologically of large, clear, fat-containing cells with large nuclei arranged in irregular strands. The resemblance of these cells to corpus luteum cells was most conspicuous, and it seems logical that this tumor and the clinical picture can best be explained as a result of tumor development with a perversion of secretion of the lutein cells.

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1770 NORTH VERMONT AVENUE

A FRATERNAL TWIN PREGNANCY

OBSERVATIONS ON THE MATERNAL OVARIES AND ON THE TWINS IN UTERO

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THAT twins of the fraternal variety originate in the fertilization of two ova is unquestioned, but whether these ova are liberated both from one ovary, or from two follicles or one, obviously can be determined only in exceptional instances. The infrequency of twins^{1, 2} is an initial handicap in the collection of such data. The difficulties are increased by the extreme rarity of opportunities to combine in the one case all the observations which are necessary for full interpretation, including the ovaries in the twin gravid woman, the twins and their membranes. In the instance here reported, it can be stated definitely that the twins are fraternal, for they are opposite sexed and dichorionic. The corpora lutea furnish evidence of their origin from ova liberated from separate follicles of the same ovary. Significantly, the corpora are so closely approximated that on superficial examination of the ovary they would have appeared as one mass.

DESCRIPTION

No history of the case is available, the specimen having been recovered without an identification mark among materials which had been long in storage in a hospital laboratory. The specimen comprises the uterus and adnexa, with a twin pregnancy advanced to about the beginning of the eighth lunar month.

The anterior wall of the body of the uterus had been slit lengthwise over a distance of some 15 cm., evidently only to admit the preservative or for a casual inspection of the interior. The uterine contents had not been disturbed except for incision of the membranes at this opening. The original slit being of too narrow a gape for the desired preliminary examinations, the exposure was increased by excising strips laterally and toward the extremities of the uterus, but with care to preserve the original relations of the membranes and fetuses. The drawing reproduced in Fig. 1, based mainly on photographs of the specimen made at this point, leaves little for description.

The total length of the fundus and corpus uteri is 25 cm. The maximum transverse diameter is 20 cm., while the maximum anteroposterior dimension is about 15 cm. These measurements obviously fall short of representing the size of the uterus before the release of amniotic fluid.

There is a single oval placenta, measuring 13 by 18 cm., the greater dimension being aligned with the long axis of the uterus. It lies on the posterior wall, and is centered slightly to the left of the midline. The umbilical cords are attached in the central area of the placenta, the cord insertion of the male fetus being 6 cm. directly superior to that of the female. Each fetus is enveloped by its separate amnion and chorion. The septum between the amniotic cavities is readily split into four layers: amnion, chorion, chorion, amnion.

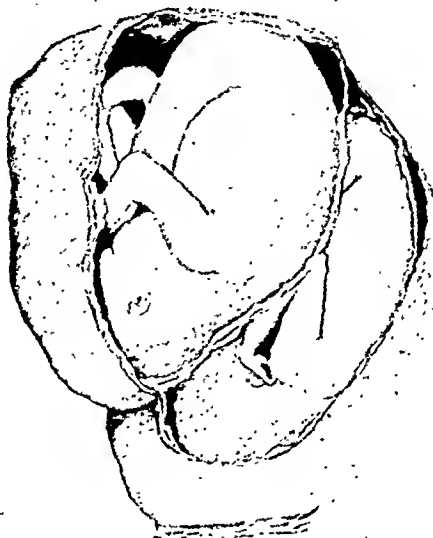


Fig. 1.—The uterus, opened anteriorly, showing the two fetuses (the male lying superiorly and more fully exposed) with their membranes. The placenta, attached to the posterior wall, is entirely covered.

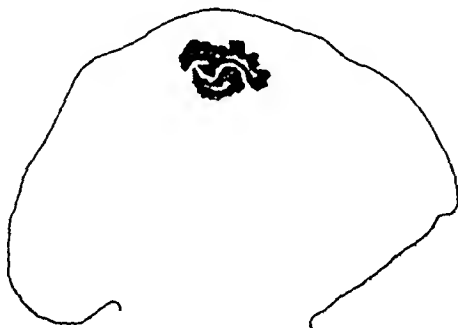


Fig. 2.—Tracing from a section of the right ovary, showing the close approximation of the two corpora lutea.

The crown-rump length of the male fetus is 21 cm., that of the female, 20 cm. The measurements point to a menstrual age of six lunar months, but the external differentiation of the fetuses (especially in hair development, disjunction of eyelids, growth of lashes, and length of nails) indicates that they are in or very near the eighth lunar month. The fact that they are twins may account for the failure to attain body sizes equal to the average of fetuses, in single pregnancies, which present equivalent advance in differentiation.

After examination, both ovaries were cut serially in celloidin, sections at close intervals being then selected and stained with hematoxylin and eosin for permanent mounting. The sections revealed no evidence of a corpus luteum in the left ovary, while the right one presented the "twin" corpora shown in Fig. 2. In maximum breadth and length this right ovary measured 30 by 42 mm., with a maximum thickness of about 10 mm. When its surface was inspected no evidence of the corpora was detectable, perhaps because of their depth as well as fading due to prolonged preservation. It is clear from the relationship of the two corpora that the follicles likewise must have been closely appressed, perhaps in a relation so intimate at the time of rupture as to produce a single massive elevation.

DISCUSSION

The occurrence of two types of twins is generally accepted: "identical," of single-ovum origin; and "fraternal," arising as in the present instance from two ova. Various suggestions have been advanced^{3, 4} in regard to the possible existence of a third type, produced by separate fertilizations of an ovum and polar body or by bispermy in a binucleate ovum, as well as classes of "identical" twins differing in embryogenesis. The twins under consideration are definitely not "identical," being unlike-sexed.

We may proceed to the ovarian evidences which call for attention in the interpretation of twin cases, considering first the number of corpora lutea. Two corpora may be frankly evident, as in the case reported by Essen-Möller,⁵ who, in performing supravaginal amputation of the uterus in early pregnancy, noted a large corpus luteum in each ovary; when the uterus was later opened, it was found to contain two embryos, their separate chorions being in keeping with the conclusion of biovular origin. In the work of Allen,⁶ on recovery of human ova from the uterine tubes, there is reported an example of double ovulation offering an exact parallel. An ovum was recovered from each tube, and a corpus luteum was present in each ovary; the ova thus may be regarded as having been the potential source of fraternal twins, both ovaries participating as in Essen-Möller's case. Other cases are on record, both for double ovulations and actual twin pregnancies, in which only one ovary is concerned.

Stein⁷ voices a caution respecting instances in which apparently only one corpus luteum is present, pointing out that a second inconspicuous corpus may be overlooked. His remark doubtless applies particularly to the inspection of ovaries at operation. Its aptness is borne out by the findings in the ovary here described. Stein's warning should be extended to cases where two corpora are observed, since a third one might pass unnoticed in the same manner.

The factor of embryonic mortality⁸ is of sufficient importance to call for attention in deductions based upon the number of corpora lutea. In this case, for example, it might be postulated that the twins originated from two ova developed in one follicle, and that if the ovum released from the other were fertilized the embryo had died and was absorbed. Such an interpretation does not call for serious consideration in the present instance, in view of the fact that a careful search of the sections of both ovaries did not disclose a single follicle containing more than one

oocyte (polyovular follicles being characteristically fairly numerous when they occur at all).

With assurance that a single corpus luteum is present, the associated twins may be of either the "identical" or fraternal variety. Wieman and Weichert⁹ report on a specimen obtained at autopsy, the uterus containing same-sexed dichorionic twins and the ovaries presenting but one corpus luteum. The authors conclude that a bi-ovular follicle had produced the ova, giving rise to these twins. The occurrence of such follicles in the human ovary is well established.¹⁰ The question then arises as to whether it is justified to relate the individuals, in cases of fraternal twins such as the one here reported, to separate follicles corresponding to the two corpora lutea. In the present case the conclusion seems to be reasonably sound; as pointed out, neither ovary contains polyovular follicles.

SUMMARY

The intrauterine relations of a pair of fraternal twins (male-female; dichorionic) near or in the eighth lunar month are described. The maternal ovaries, prepared histologically, show that the twins arose from ova in separate follicles of the right ovary, as indicated by the presence in it of two corpora lutea and the absence of a corpus in the left ovary. Since the two corpora lutea are very closely approximated it is quite probable that surface inspection of the ovary would have failed to disclose the double nature of the mass. Inspection of the ovarian surface at laparotomy is the only feasible observation in some twin cases, and the present finding points a warning against assuming that the full number of corpora lutea is invariably noted by this means.

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To the heretofore reported approximately 200 cases of round ligament tumors, the authors add five new observations. They were an endometrioma, a fibroma, two cystic tumors (a congenital multilocular cyst and a cystic hygroma), and a capillary hemangioma with areas suggestive of benign angioendothelioma. The latter condition seemingly has never before been recorded in literature. The two cystic tumors were associated with indirect inguinal hernias.

The most common type of round ligament tumors are fibromas, followed by endotheliomas in regard to frequency.

HUGO EHRENFEST.

BILATERAL DERMOID CYSTS COMPLICATING PREGNANCY*

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THIS case is presented not only for its scientific interest, but also because of the multiplicity of complications in a patient twelve weeks' pregnant.

H. K., white, 33 years of age, gravida vi, para i, was admitted to St. Mary's Hospital, Brooklyn, N. Y., April 1, 1941, complaining of pain in the left lower abdomen and of vaginal bleeding.

The last menstrual period began Dec. 24, 1940. It was normal in character and lasted the usual three days. The patient was well until Jan. 22, 1941, on which date she began to have spotty vaginal bleeding. This spotting was present daily until Feb. 20, 1941. She was then free of bleeding for about one month, but from March 17, 1941, up to the time of admission to the hospital there was daily recurrence of the spotting.

One week prior to entrance into the hospital the patient was seized with severe, cramplike pain in the left lower quadrant of the abdomen, and she felt as if she were going to faint. Although the pain diminished in severity, a residual soreness continued in the left lower abdomen.

Abdominal examination revealed extreme tenderness, with some tenderness, in the left lower quadrant. A tender mass could be palpated about two and one-half fingerbreadths above the symphysis.

Vaginal examination disclosed a soft uterus which was approximately three times normal size, with an extremely tender mass filling the posterior cul-de-sac. A larger, cystic mass was palpated in the left lower quadrant which was movable and tender.

A provisional diagnosis of an unruptured ectopic pregnancy with a left ovarian cyst was made and laparotomy advised. The blood count showed 4,150,000 red blood cells, 85 per cent hemoglobin, neutrophils 60 per cent, and lymphocytes 38 per cent. The urine was negative. Laparotomy on April 4, 1941, revealed the following: (1) Right dermoid cyst the size of a large orange, filling the posterior cul-de-sac. (2) Left dermoid cyst the size of a grapefruit, with a twisted pedicle, rising above the pelvis and situated in the left lower quadrant of the abdomen. (3) An intrauterine gestation of three months' duration.

A bilateral total oophorectomy was easily performed under basal avertin anesthesia, supplemented by nitrous oxide, oxygen, and ether.

The postoperative care included: (1) Morphine sulfate, gr. $\frac{1}{4}$, every four hours for two days. (2) Progesterone, 5 mg., t.i.d., from April 4 to 7, 1941 (three days). Progesterone, 5 mg., b.i.d., from April 7 to 12, 1941 (five days). Progesterone, 5 mg., u.i.d., from April 12 to 16, 1941 (four days). (3) Progesterone, 5 mg., once a week until May 9, 1941 (one month). (4) Wheat germ oil, 2 dr., t.i.d., from April 12 to 16, 1941.

The postoperative course was entirely uneventful and there was no morbidity. The patient was discharged from the hospital May 16, 1941.

*Presented at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

Follow-up visits in the clinic revealed that pregnancy was progressing satisfactorily. The patient was delivered of a full-term living female child, Sept. 27, 1941, by low prophylactic forceps, 176 days after operation. Lactation of the newborn was normal.

Pathologic Report.—The specimen consisted of two cysts, one about the size of an orange; the other, somewhat elongated, was larger, about the size of a grapefruit. Both cyst cavities were surrounded by a thickened, almost transparent capsule. They were filled with a large amount of yellowish, caseous, cheeselike material in which were found numerous clumps of thickened, brown to yellowish, hair. Both cysts resembled dermoid cysts in type.

Microscopic sections showed a fibrous cyst wall which, in some places, was outlined with several layers of cuboidal epithelium. There were a few remnants of atrophic sebaceous glands present. Both cysts were similar in structure.

DISCUSSION

Dermoid cysts account for 10 per cent of the cystic neoplasms of the ovary (Novak¹), 25 per cent being bilateral. Dermoids are benign cystic ovarian tumors characterized by a predominance of ectodermal elements containing sebaceous material, hair and other forms of ectoderm and occasionally some mesodermal elements.

Bilateral ovarian dermoids complicating pregnancy, in which bilateral ovariectomy is performed, are of especial interest because of their rare incidence. The available literature reveals only 46 reported cases. Andrews and Nicholls,² in an exhaustive review of the literature, found 43 cases and report a case of their own. King³ and Southward, Jr.,⁴ have each reported one case. Thirteen patients, not including the case reported herein, were operated upon within the third month of pregnancy. The successful conclusion of pregnancy in 11 of these (two having aborted) initiates an interesting endocrinologic discussion.

Experimental evidence, as shown by the literature, reveals the belief that the placenta completely assumes the hormonal functions of the ovary. Not only has progesterin been found in the placenta, but estrogen fractions have also been recovered. Smith and Smith⁵ and their co-workers have presented exhaustive studies of hormone assays in both the normal and abnormal types of pregnancies, including the toxemias. These hormonal reports evaluate in detail the total amounts of chorionic gonadotropin, estrogen and progesterin excreted daily during pregnancy. It is interesting to note at this point the tremendous advantage that the combination of research worker and clinician has over the purely scientific or clinical investigator, because he has at hand the statistical findings to support his clinical observations.

Seegar and Delfs,⁶ in a study of pregnanediol excretion following bilateral oophorectomy in early pregnancy, report cases "in which the corpus luteum of pregnancy was removed on the one hundred and twentieth and fifty-fourth days, respectively, and pregnanediol excretion subsequently remained within normal limits. These cases seem to lend additional support to the theory of a placental origin for progesterone during pregnancy. However, in both cases functional ovarian tissue remained." They also report a case of their own in which pregnancy continued normally after removal of all ovarian tissue on the fifty-sixth day of gestation. Serum gonadotropin and pregnanediol assays were done in this particular case. The former was found to be within normal limits as compared to normal pregnancy. The pregnanediol assays, how-

ever, were lower than normal, varying from 3.5 mg. per twenty-four hours in early gestation, to 20 mg. at the ninth month, instead of from 5 to 100 mg.

Supported further by the successful conclusion of pregnancy in the 11 reported cases (12 including our own) in which bilateral oophorectomy was performed within the third month, it is our contention that the placenta, once it has been well established, plays the all important role of custodian of gestation, superseding the corpus luteum. The exact period at which this transfer takes place has not as yet been definitely established. Jones and Weil⁷ report that progesterin production begins to take place about the sixtieth day of pregnancy. It is safe to assume that total transfer of function with complete safety to the fetus is assured at least by the ninetieth day following conception. With this in mind, the value of progesterin therapy in our case is problematic. However, used as a complement to the already existing hormones, progesterin probably acted as a sedative to the uterus. The important role of progesterin in lessening uterine sensitivity and contractility has already been established by Lubin, Reynolds and Clarke⁸ in post-partum after-pains and by numerous others in threatened abortion. It probably also bridges the gap of diminished hormonal production following the trauma of an operative procedure. The synergistic action of estrogen and progesterin, as brought out by Smith and Smith in 1940, would have warranted a trial of therapy. That is to say, that the therapeutic action of progesterin would have been enhanced by the simultaneous use of estrogenic hormone.

CONCLUSIONS

1. Another instance of pregnancy complicated by bilateral dermoid cyst, followed by bilateral oophorectomy, has been added to the 46 cases already reported in the literature.

2. An attempt has been made to enhance the established belief and advance it to the stage of factual conclusion that the placenta takes over the complete role of the ovary at about the third month of gestation.

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145 SIXTH AVENUE
225 BAY RIDGE PARKWAY

FIBROMA OF THE OVARY ASSOCIATED WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME)*

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IN 1937, Meigs and Cass¹ called attention to the clinical entity of fibroma of the ovary accompanied by a serous transudate in the abdominal and in one or both pleural cavities. They reviewed the seven cases that had been reported in the past twenty-five years and shortly thereafter added eight others.² They were not the first to record this syndrome, since Owen³ and Hoon,⁴ in 1923, described the association of an ovarian fibroma with hydrothorax and ascites. Meigs and Cass,¹ however, emphasized that such cases could be cured by removing the ovarian tumor in spite of the grave appearance of the patient.

Ovarian fibromas comprise 1 to 4 per cent of all ovarian tumors. A fair average would appear to be 2 per cent.⁵ Ascites alone is a frequent finding in such tumors. Only 18 cases have been reported in the literature of ascites and hydrothorax occurring with these neoplasms, in which the fluid disappeared spontaneously following removal of the mass. It is fair to presuppose that many more cases have undoubtedly occurred but have not been reported.

In the recorded cases of Meigs' syndrome, the patients' ages varied from thirty-one to sixty-four, though the majority were at or near the menopause. As a rule, the chief complaint was dyspnea or a dragging sensation in the lower abdomen with the knowledge of a mass in that region for varying periods of time. In one case, the mass was known to have existed for eight years. Occasionally, abdominal paracentesis was necessary before the tumor could be felt. Cachexia was common, due to rapid dehydration. The correct diagnosis was usually difficult to make, since the condition closely resembles pelvic malignancy.

There were two deaths in the 18 reported cases. The actual cause of death was difficult to determine. One patient was never operated upon, while in the other, the fibroma was complicated by pregnancy with eclampsia. In both instances, it was apparent that delaying the operation contributed to a more rapid demise.

Bomze and Kirschbaum⁵ pointed out that many of these patients were hospitalized for symptoms suggestive of heart failure. In addition, several had electrocardiographic findings substantiating the diagnosis of heart disease. These men suggested that the fluid might be caused by the added strain upon the heart due to pressure by the heavy tumor in one who is just within the bounds of compensation; or it might be due to an interference in the pelvic and lower abdominal circulations. Significantly, the fluid rapidly re-accumulates following thoracentesis or paracentesis but spontaneously disappears following surgical removal of the tumor. In one case, 5 thoracenteses were done in four weeks with a

*Read at a meeting of the Brooklyn Gynecological Society, December 5, 1941.

total of 8,900 c.c. of fluid removed.⁹ The decompensation theory does not adequately explain the presence of the transudate, yet, we have no better one to offer.

The fluid has been found sterile despite many attempts to isolate organisms by cultural or animal inoculation methods. Malignant cells have never been demonstrated. The physical and chemical characteristics are those of a transudate. Blood studies, especially serum proteins, are within normal limits.

The fluid is more frequently found in the right pleural cavity though it has been noted in the left pleural sac on several occasions and in one case was bilateral. The location of the fluid bears no relationship to the position of the tumor although the right ovary is most frequently involved. In 3 cases, both ovaries were the seat of fibromas.



Fig. 1.—On admission, x-ray revealed a pleural effusion on the right side extending to the sixth rib in the axillary line.

Pathologic examination of the neoplasm revealed it to be an encapsulated cellular fibroma. Areas of cystic degeneration and necrosis are common. Following removal of the tumor, recurrences have not been reported though cases have been followed for as long as twenty-seven years.

Such a case was recently observed at the Kings County Hospital and is being reported because it represents this syndrome occurring in the oldest patient on record.

CASE REPORT

Mrs. A. M., a 73-year-old, white woman, was admitted to the Medical Service of the Long Island College Division of the Kings County Hospital on March 4, 1941. For the past three months she had complained

of shortness of breath and swelling of the abdomen. Her troubles started in November, 1940, when she experienced increasing dyspnea on exertion and noted that her abdomen was becoming larger. Two years ago, she had been hospitalized for "an episode of decompensation" similar in all respects to her present difficulties. The menopause had occurred at the age of 48, and there had been no bleeding or discharge since.

On admission, the temperature was 99.8° F., pulse 75, respirations 20, and blood pressure 158/85. She was dyspneic, orthopneic, and markedly cyanotic. Physical examination revealed the following significant findings: dullness over the entire right upper chest down to the third rib with flatness from this level to the base, anteriorly and posteriorly. No



Fig. 2.—X-ray taken before operation and after thoracentesis showed fluid in the right side extending to the seventh rib in the axillary line.

breath sounds were audible over the right chest though the left side was clear. A soft systolic murmur was heard at the apex and the heart was slightly enlarged to the left. The abdomen was markedly distended, the percussion note flat, and a fluid wave with shifting dullness was present. Both feet, ankles, and legs up to the knees were markedly edematous.

The urine was negative. The white cells numbered 18,500 with 68 per cent polymorphonuclear leucocytes. The red cells numbered 5.25 million and the hemoglobin was 78 per cent. The blood urea was 27 mg. per cent and the blood Wassermann was negative. The electrocardiogram was reported as showing extensive myocardial fibrosis. Roentgenogram of the chest (Fig. 1) revealed a pleural effusion on the right extending to the sixth rib in the axillary line with elongation and calcification of the aorta and preponderance of the left ventricular contour of the heart.

The medical staff was of the opinion that the patient was suffering from decompensation due to hypertensive cardiovascular disease. She was given mercurial diuretics and digitalized. Moderate diuresis was established, and by March 8, the peripheral edema had almost completely disappeared. The abdominal fluid decreased sufficiently to permit the palpation of a large mass. Some fluid was removed from the chest for diagnostic purposes and revealed many red cells though no lymphocytes or malignant cells were seen. A gynecologic consultant, on March 25, described the mass as being eight inches in diameter, firm in consistency, freely movable, slightly nodular, insensitive and originating from the pelvis. Its upper limit extended slightly above the umbilicus. The

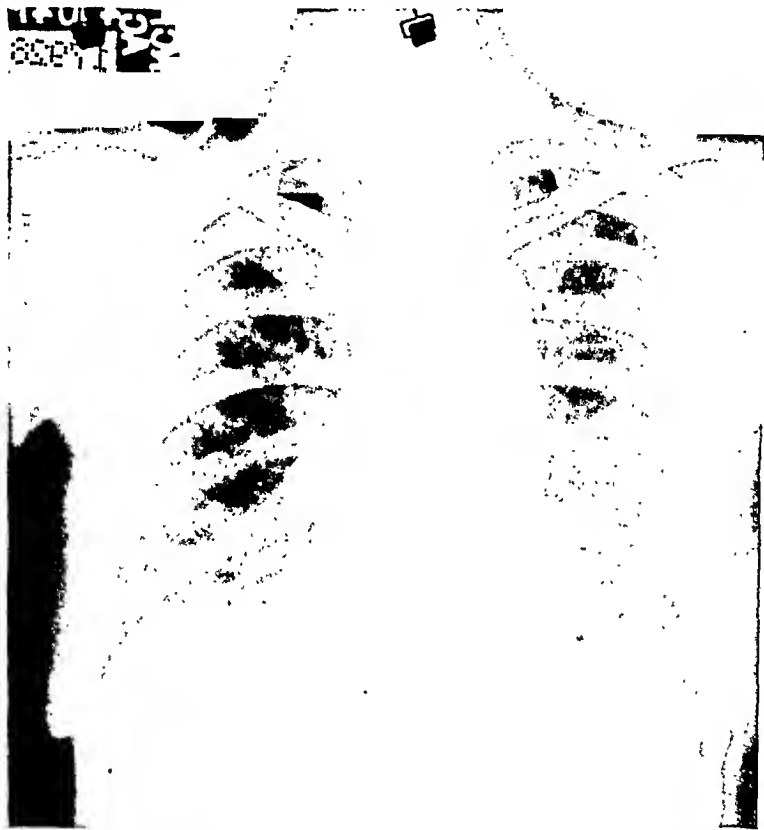


Fig. 3.—On the sixth day postoperatively there was no fluid in the right pleural sac.

pelvic examination disclosed a senile vaginitis with the cervix flush with the vaginal vault. The uterus could not be outlined. The abdominal mass was found to lie in the right fornix. At this time, the white cells had fallen to 12,200 with 82 per cent polymorphonuclear leucocytes; the red cells numbered 4.8 million and the hemoglobin was 91 per cent. The sedimentation time was over eighty minutes. A second roentgenogram of the chest (Fig. 2) showed a slight decrease in the pleural effusion on the right side.

On March 28, 1941, the patient was taken to the operating room and under 1 per cent procaine anesthesia the abdomen was opened through a six-inch suprapubic midline incision. The peritoneal cavity contained about 400 c.c. of straw-colored fluid. The uterus was small, posterior and lying in front of it, and extending upwards to a point 6 cm. above the umbilicus was a large, globular, gray-white, firm tumor of the right

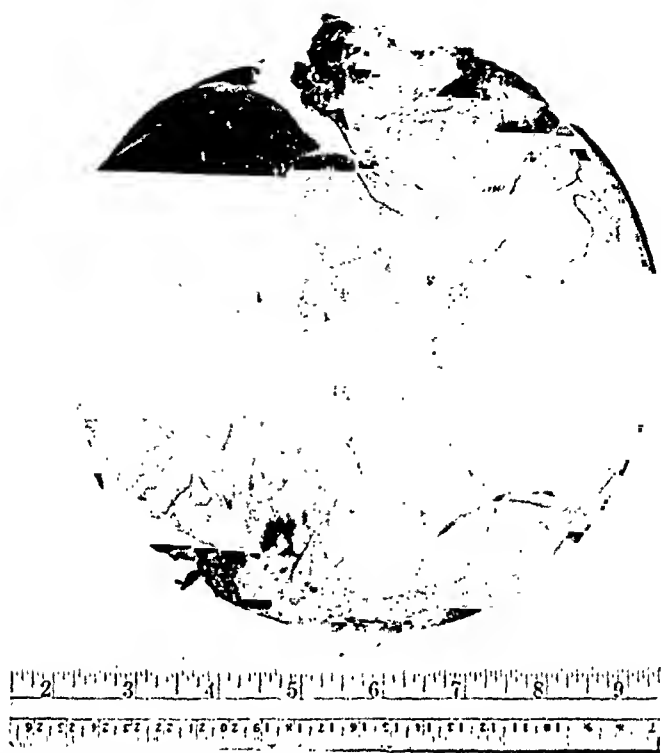


Fig. 4.—View of tumor. External surface was nodular, gray white in color, and the capsule was intact with many dilated veins coursing through it.

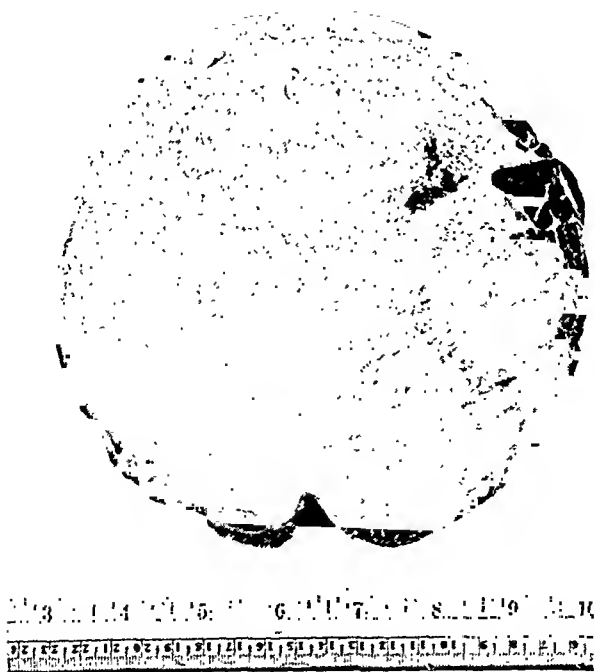


Fig. 5.—The cut surface of the tumor was gray white in color with a moderate-sized area of interstitial hemorrhage.

ovary. The fluid was aspirated, the neoplasm removed, and the abdomen closed with through-and-through black silk sutures.

The postoperative reaction was slight; the temperature rose to 100.4° F. and the pulse to 110 for the first two days. Gradually, these fell to normal and after forty-eight hours remained normal. On the sixth postoperative day, x-ray of the chest (Fig. 3) revealed that the fluid had entirely disappeared. On the tenth postoperative day, the patient was allowed out of bed, and on April 9, 1941, she was discharged in excellent condition. Since then, she has been seen on several occasions and has had no complaints. Neither the ascites nor the hydrothorax have recurred.

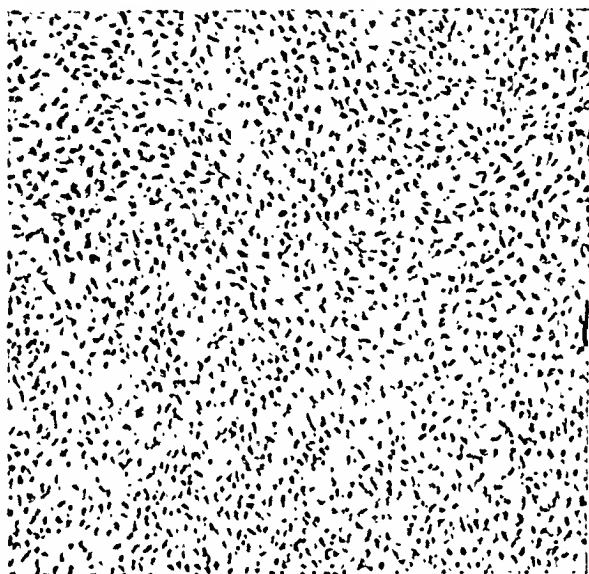


Fig. 6.—Microscopically, the neoplasm was comprised of broad sheets of spindle or oval fibroblasts.

Pathologic Report.—The specimen consisted of a large, oval mass measuring 18 by 16 by 10 cm. (Fig. 4). The surface was smooth, glistening, gray white in color with many small veins and venules coursing through its capsule. On section (Fig. 5) the tumor was made up of white whorls of fibrous tissue containing a large area of interstitial hemorrhage.

Microscopically, sections from various portions of the tumor revealed the same architecture and consisted of bundles of fibroblasts whose component cell was either oval or spindle in shape, contained moderate cytoplasm and an oval or spindle-shaped nucleus that took a deep stain (Fig. 6). In some areas, edema was prominent, producing a myxomatous-like appearance. Special stains failed to reveal the presence of fat.

Diagnosis: Fibroma of the right ovary with focal areas of hemorrhage and edema.

COMMENT

Despite suggestive signs and symptoms of cardiac disease and electrocardiographic evidence of myocardial fibrosis, this patient has been cured by the removal of the ovarian neoplasm. Postoperatively, the dyspnea, cyanosis, edema and fluid in both the pleural and abdominal cavities

entirely disappeared and have not recurred although she is actively engaged in housework and takes no medication.

The differential diagnosis must include pelvic malignancy with pleural and peritoneal metastases, tuberculosis, and cardiac failure. Here, only a tuberculous infection was easily excluded. Had operation been delayed, the result might have been fatal. Instead a cure was obtained. Consequently, it behooves the clinician to exercise extreme caution in offering a prognosis in those cases where a pelvic mass is associated with ascites and hydrothorax.

SUMMARY

1. A discussion of 18 previously reported cases of Meigs' syndrome is given.

2. Another case is reported in a woman of seventy-three years, the oldest of any of the reported cases.

3. The importance of establishing a diagnosis followed by surgical removal of the tumor is emphasized.

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AN EVALUATION OF A PARTICULAR MODE OF THERAPY OF TRICHOMONAS VAGINALIS

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THE purpose of this communication is first to correlate the hydrogen ion concentration of the vagina with the presence or absence of *Trichomonas vaginalis*, and, second, to evaluate the results of a particular mode of therapy.

Hesseltine's¹ communication brings the subject in many of its aspects to date. The pathology has been presented by Kessel and Gafford.² They biopsied the vaginal mucosa, including the petechial spots, and showed that the necrotic areas, only, harbor the flagellate. These workers have also shown the absence of the lactobacillus in trichomonas. Trussell and Plass³ have infected women with pure cultures of trichomonas vaginalis. The work of Feo and collaborators³ demonstrated that the *Trichomonas (hominis) intestinalis* is not a source of the infection.

They also have shown that the infection can be transplanted from fresh smears taken from the vagina, whereas pure cultures of *Trichomonas vaginalis* rarely infect.

From the data herein presented one must assume that acidity plays a definite part in this disease. The pH of the vagina was determined by means of the Beckman glass electrode which was inserted through a speculum, thus making direct contact with the vaginal wall. This method gave very accurate readings. For practical purposes the results using nitrazine indicator paper correlated well with the Beckman potentiometer readings. Therefore, in 50 per cent of the cases the nitrazine indicator method was used.

During this study, 145 pH determinations were made and the presence or absence of the flagellate noted. These are tabulated in Table I which shows that the trichomonas could be demonstrated in 13 out of 93 cases (20 per cent) at a pH of 5.5 or below, whereas above a pH of 6 their presence was demonstrated in 37 out of 52 cases (60 per cent). As shown, the flagellates are occasionally found at a pH below 5.5 and can be absent above a pH of 6 even though previously present in a patient with a pH of 6 before treatment. Trussell and Plass⁴ observed that the trichomonas was better cultured above a pH of 5.5.

TABLE I

pH	POSITIVE	NEGATIVE
8	0	0
7.5	5	1
7	7	7
6.5	8	2
6	17	5
5.5	4	16
5	4	16
4.5	5	44
4	0	4

The treatment consisted of a douche containing one teaspoonful of lactic acid per quart of water. This gave a solution with a pH around 3.2. Following the douche, a compressed tablet containing 3.5 Gm. of B-lactose and enough citric acid and sodium bicarbonate to produce about 300 e.e. of CO₂ was inserted into the vagina. The gas produced served to spread the lactose throughout the vagina. It was necessary for the patient to wear a perineal pad, since the gradual solution of the lactose caused considerable drainage. It is believed that the lactose is utilized by bacteria to form more lactic acid, hence continuously keeping the vagina at a low pH. In twelve hours another douche was taken followed by the insertion of another tablet. This procedure was followed for twelve days; the patient was instructed to take no douche for two days before her visit. A few patients complained that the discharge from the tablet caused irritation and a burning sensation.

A total of 35 patients were followed four months to one year at bi-monthly periods during the active stage, then monthly thereafter for three months. Fifteen of the patients were cured after two weeks' treatment, 4 after four weeks, 2 in six weeks, 3 in eight weeks, 1 in three months, 1 in four months, 3 in five months, and 1 in eleven months. There were four failures. Twelve patients had recurrences after apparent cure. In this series of cases there were 3 post-partum patients, 1 in early and 1 in late pregnancy, 2 having had recent abortions, 3 with chronic salpingitis, 3 harboring organisms following intercourse, 1 in the menopause, and 1 with chronic cervicitis. Most of the two-week cures were uncomplicated cases. In following these patients several reasons for failure to respond to treatment were noted and when corrected by the patient a cure usually followed. One of the reasons for unresponsiveness to treatment was a failure to insert the tablet well up into the vagina. Another was a lack of persistence in treatment, and a third was failure to carry out the treatment during a menstrual period. This last cause for failure was probably the most common, and is well accounted for by the fact that the vagina is relatively more alkaline during the time of catamenia.

A series of 27 cases using floraquin* tablets instead of the B-lactose tablets was similarly studied with comparable results.

SUMMARY AND CONCLUSIONS

The optimum pH for inhibition of *Trichomonas vaginalis* in the vagina is 5.5 and below. This hydrogen ion concentration can be maintained by means of dilute lactic acid douches and B-lactose. Eighty-eight per cent of the patients so treated were cured. Unknown factors account for the 12 per cent of failures.

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*The author wishes to thank the G. D. Searle and Company for their generous cooperation in supplying floraquin tablets for this study.

TREATMENT OF TRICHOMONAS VAGINALIS VAGINITIS WITH NEGATAN (NEGATOL)

WILLIAM FILLER, B.S., M.D., F.A.C.S., NATHAN DREZNER, B.S., M.D.,
AND FRANK H. ADAMO, B.S., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University,
College of Medicine and Bellevue Hospital, Gynecological Clinic)

FOR some years studies have been conducted in the gynecologic clinic at Bellevue Hospital in the treatment of *Trichomonas vaginalis* vaginitis, utilizing a number of different preparations and modes of therapy. No one therapeutic approach had ever proved so successful as to leave no room for another.

Since 1938, a new preparation, negatan (Negatol, Lilly) has been used in this clinic. The chemical and pharmacologic characteristics of negatan have been reported in an article¹ by the authors on the treatment of cervicitis with the same drug.

Eighty-seven cases of *Trichomonas vaginalis* vaginitis were treated in the following manner:

After a positive diagnosis was made by microscopic examination of the discharge, the vagina was cleansed with green soap, and dried. The vagina was then insufflated with negatan powder. The patient was instructed to douche with a tablespoonful of vinegar in two quarts of hot water the next night, following which she inserted a 20 per cent negatan suppository. This was repeated each night for one week, when she returned to the clinic for another insufflation and observation. Patients were often lax in returning regularly. However, no effort was made to record statistically such laxity. The criteria for cure consisted of three negative spreads after three successive menstrual periods without treatment during this time.

The results obtained in the treatment are given in Table II.

TABLE II

		AVERAGE NUMBER TREATMENTS	DURATION AVERAGE NUMBER DAYS
Cures	44 or 51%	8	103
Marked improvement (Symptomatic cure; at least one negative spread, but not observed long enough to be declared cures)	38 or 44%	7	66
Failures	5 or 5%	16	180
Total number of cases	87		

Although negatan failed to furnish uniformly good results in the treatment of *Trichomonas vaginalis* vaginitis, nevertheless, the results of this therapy are excellent in a condition which is often resistant to treatment.

The simplicity of the method, the relatively small average number of treatments required, and the absence of untoward effects were factors to recommend negatan. In addition, the time of treatment was short when one considers that an additional period of observation of approximately sixty days' duration was necessary in order to declare the patient cured.

In conclusion, the results of the treatment of 87 cases of *Trichomonas vaginalis* vaginitis with the new drug are sufficiently gratifying to recommend its use in the care of this often refractory condition.

REFERENCE

1. Filler, William, Drezner, N., and Adamo, F. H.: AM. J. OBST. & GYN. 43: 897, 1942.

A CLINICAL NOTE ON THE USE OF SULFANILYLGUANIDINE IN MYCOTIC VAGINITIS

J. L. PINKSTON, M.D., AND JOHN C. BURCH, M.D., NASHVILLE, TENN.

(From the Department of Obstetrics and Gynecology, Vanderbilt University
School of Medicine)

THE report by Marshall, Bratton, White, and Litchfield* of a reduction in the bacterial flora of the gastrointestinal tract following the oral administration of sulfanilylguanidine suggested the possibility of a similar action on the vaginal flora. In order to observe the effect of this drug in diseases of the vagina a random group of cases comprising the various forms of vaginitis was selected. The vagina was first cleansed with green soap and water, dried, and then insufflated with 3 Gm. of sulfanilylguanidine.† It was soon seen that this drug had a definitely beneficial effect on that form of vaginitis associated with mycotic infections. Since that time we have treated all of our cases of mycotic vaginitis with this drug. In most cases the drug has been applied by the patient to the posterior fornix of the vagina in gelatin capsules. Usually the application of 1 Gm. each morning and night, for a period of two weeks, will suffice. To date 20 patients have been treated by this method. In all cases the diagnosis was confirmed by a vaginal culture. Three patients reported symptomatic relief, but the cultures remained positive after treatment. Eight patients reported complete symptomatic relief but were unavailable for cultures at the conclusion of treatment. Nine patients reported complete symptomatic relief, and the cultures became negative for mycotic organisms. No evidence of toxicity of the drug was observed.

*Marshall, Bratton, White, and Litchfield: Bull. Johns Hopkins Hosp. 67: 163, 1940.

†Supplied to us through the courtesy of Dr. David Brice of Lederle Laboratories.

Special Article

OBSERVATIONS ON THE ART OF MEDICAL ILLUSTRATIONS*

FREDERICK H. FALLS, M.D., CHICAGO, ILL.

IF ONE reviews the fields of art and medicine critically, two things stand out clearly. First, that many of the great artists were especially interested in the various phenomena of obstetrics and gynecology and second, that many of the great medical men tried to express their ideas in drawings no matter how crude and for the particular purpose of teaching their fellow physicians.

The best of the early attempts at art reproduction of men and events are the low bas-reliefs of the Egyptians and Assyrians. Later the Greeks used the high bas-relief and sculpture in the round. The designs were made in stone because of its endurance and availability. The earliest efforts were necessarily crude.

After the fall of Greece and through the Dark Ages very little was contributed to art of any kind throughout the world.

With the beginning of the Renaissance, there was a revival of art and the dawn of modern medicine. Leonardo da Vinci was the father of all medical art. His indomitable spirit and indefatigable mind led him to dissections of all kinds which he recorded carefully with full notes, in pen and ink and other media. His sketches which have come down to us are masterpieces of art. It was he who said: "The farther science develops the nearer it approaches art; the higher art develops the nearer it approaches science."

The first great team of medical illustrators with which we are familiar were Vesalius, the great anatomist, and Jan van Calcar, who made his drawings. They were markedly influenced by da Vinci's work and made many very creditable anatomic sketches.

Michelangelo, Luca della Robbia, and many other Renaissance artists concerned themselves with the depiction of motherhood, because of the religious importance of the Madonna and Christ child.

John and William Hunter left many sketches and drawings as records of their observations. So on down to our time when medical illustration has become a specialized field of art.

The average specialist in obstetrics and gynecology has had little or no opportunity to make a study of or even come in close contact with high grade medical illustrations. Even in the majority of medical colleges of the country the development of an art department has received scant attention or none at all. Almost universally, however, a medical specialist finds himself sooner or later in need of the services of a medical illustrator in connection with the production of books, lectures,

*Presidential Address at the fifty-fourth Annual Meeting of the American Association of Obstetricians Gynecologists and Abdominal Surgeons, Hot Springs, Va., September 11 to 13, 1941.

and magazine articles for publication. Since competent artists are so rarely found among medical specialists, he is fortunate indeed who can secure the advice and services of a skilled artist to assist him in projecting his ideas in a clear, dignified and forceful manner. Even when a good artist can be secured, the problem is not completely solved, for it is essential that the medical man appreciate both the possibilities and limitations of various forms of medical art, and that the artist have sufficient clinical experience and knowledge of the subject in hand to comprehend what the doctor wants to have emphasized. This teamwork is an essential part of good medical illustration in the field of obstetrics and gynecology.

The subject which I wish to present to you today is one which has held considerable interest for me for a number of years. To avoid any misconception, I wish to say that personally I have absolutely no artistic training or ability and to add that neither is essential to an understanding of this subject if one spends sufficient time to become acquainted with the problems and possibilities.

I have had the good fortune to have been rather closely associated with Mr. Tom Jones, Director of the illustrations studio of the College of Medicine, University of Illinois, for the past fifteen years. It has been most interesting and instructive to see first hand the work done by him and by the group of young artists associated with him.

One of his former students, Miss Charlotte S. Holt, has worked with me continuously for the past five years in preparing illustrations for a textbook, lantern slides for graduate and undergraduate teaching, and in the making of lay and professional exhibits for the educational program in maternal welfare in Illinois. Her collaboration has assisted in no small measure in making the visual educational part of the program outstanding.

From these contacts certain concrete ideas have been gleaned which I feel are of considerable value to medical men in the preparation of scientific communications, and which I wish to share with you with your permission.

In general, it may be said that medical illustrations fall roughly into several groups: photographs, line drawings, halftones, wash drawings, water colors and various types of models and charts for exhibit purposes.

CHARTS

One of the simplest and also most abused forms of medical illustration is the chart. There is a great temptation to crowd too much information on a single chart. Frequently also, the fault lies with the arrangement of the information on the chart rather than the amount of subject matter displayed.

To be of maximum value charts must have letters of sufficient size and simple style which stand out clearly enough to be read by the average person without eyestrain. The lettering should be clear, simple, and contrast sharply with the color of the background. For emphasis, when making lantern slides and charts for exhibit purposes, it may be of advantage to have certain sentences or paragraphs begin with words in color. Another device is to underline with colored or black lines important words or sentences.

Most charts must be framed if used for exhibit and teaching purposes since, if this is not done, they deteriorate rapidly due to handling, falling, packing, and other necessary usage. To minimize this risk we have found that covering the chart with pliofilm or similar transparent material and placing in a simple wooden frame will answer the purpose very nicely. Such charts are relatively lighter, less expensive and more durable than when glass is used for covering purposes.

Graphs are a form of chart and are subject to the same general rules. Frequently they are too crowded for comfortable quick reading, and as a result the information which they contain is difficult to appreciate by the average lay or professional audience, especially when they are presented in the form of lantern slides. In the interest of clarity the lines

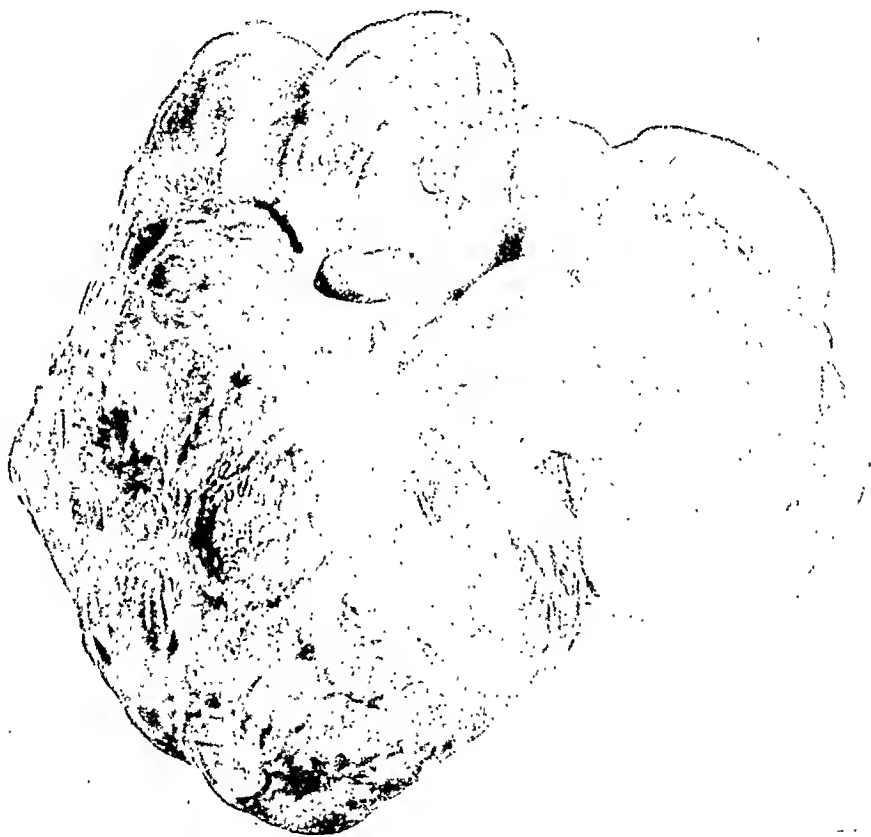


Fig. 1.—Example of black and white photography by Lawrence A. Toriello.

of the graph should not cross frequently if this can be avoided. Much writing or lettering in the body of the graph is undesirable. Both charts and graphs should have a clearly worded brief descriptive title, and if necessary an explanatory footnote may be added to clarify certain points.

PHOTOGRAPHS

Photographs are of great value for book or other illustrating purposes but, while most easily produced, they are the most undeveloped type of medical pictures. To be good illustrations and have scientific value they must be carefully taken of subjects correctly posed and illuminated. Snap shots of lesions and patients are for the most part useless. Good color photographs are even more difficult to make and are less satisfac-

tory because the colors are frequently exaggerated and not at all like the original in tonal value. Another objection is that with the present emulsions they tend to fade and change color in a few months or years, which seriously affects their permanent value. A great deal of research is being done to solve these problems and much improvement is to be expected in the immediate future.

Another weakness of the photograph is that the camera has no sense of selection and takes in everything within range on about the same dead level, whether of importance or not. In a drawing on the other hand, the artist can emphasize what the doctor wants brought out and subordinate the relatively unimportant details. Photographs have the advantage of speed in making and of usefulness as evidence in supporting some claim by the writer. They are also relatively inexpensive and have therefore the advantage that several photographs can be made of a given lesion and the best one selected, whereas, one drawing must, as a rule, suffice because of the expense involved in the production.

In illustrating a subject or lesion which is rarely encountered clinically and therefore difficult to present to the artist for first hand study, photographs of such lesions may be very valuable to the clinician in getting his ideas before the artist.

Photographs can also be enlarged or "blown up" for certain purposes and when printed on the proper type of paper can be tinted and made to appear almost like an original pastel or water color drawing. (Lantern slides can be made in black and white and then tinted with aniline dyes or colored photographs may be taken directly.)

Photographs of operative procedures taken at the time of operation have proved rather disappointing. It is difficult in many cases for the operator to pause at the precise point in the operation that he wishes recorded to allow the photographer sufficient time for correct focusing of his camera, the necessary light adjustment for proper illustration of the part to be photographed for his purpose, and the posing of instruments and personnel for the best results in the picture. Furthermore, unless the photographer is especially trained in operating room technique, there is considerable danger of serious contamination of the operative field.

The chief advantage of photographs is in depicting inanimate subjects, for example, an operating room setup; a complicated machine, such as the Drinker respirator, or to show the outside of a building, an operating room, or special instruments.

Photomicrographs are very valuable and can be displayed in black or white, or can be hand colored by an artist. Colored photomicrographs can also be made which are open to the same objections cited above for color photographs in general. Proper illumination of the slide and careful selection of the field to be photographed require time, patience and cooperation between the photographer and the surgeon.

The x-ray print is useful in illustrating certain phases of anatomy and pathology not otherwise easily demonstrated. It has the disadvantage however of being difficult to reproduce in half tone because of the frequent poor contrast in the original even when strongly illuminated. As a result retouching by hand by an artist is often necessary to secure the desired detail, which detracts somewhat from the validity of

the photograph. The x-ray illustrations in most textbooks are frequently very disappointing because these factors have not been taken into consideration by the writers.

Recently considerable advance has been made in photographing lesions of the cervix and vagina. For this purpose colored photographs have been used as well as black and white. The results have not been altogether satisfactory, however, because of the difficulty inherent to the problem which probably never can be completely eradicated, namely, that if the object to be emphasized, such as the anterior lip of the cervix, is in sharp focus, necessarily the rest of the field must be blurred, because it must be out of focus and therefore appears distorted.

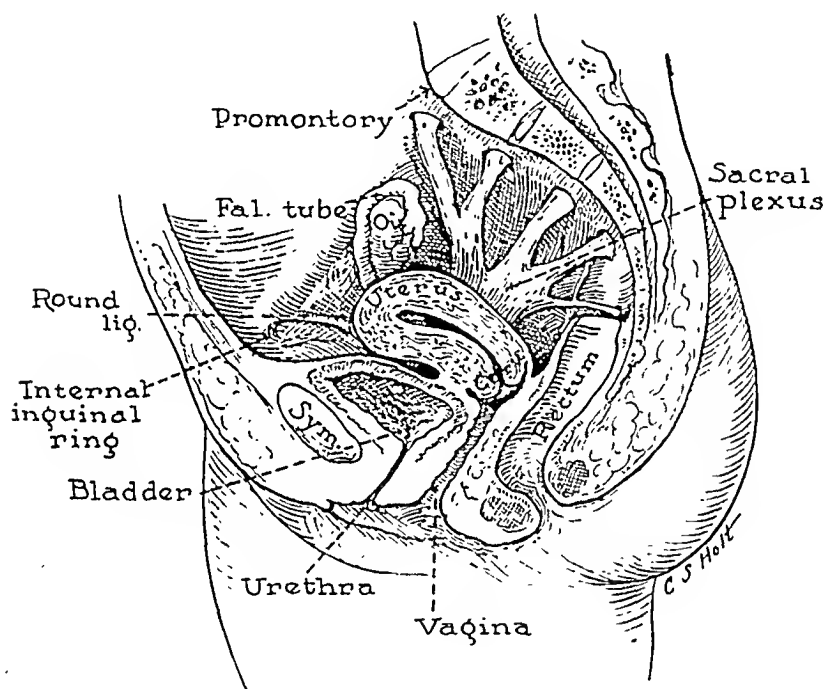


Fig. 2.—Example of a pen-and-ink drawing.

PEN-AND-INK DRAWINGS

The pen-and-ink drawing is very effective for many subjects and is often preferable to any other type of drawing. It has the advantage of sharpness of detail, simplicity and if well done carries the message with the least possible effort on the part of all concerned. To be effective such drawings should not be too complex and detailed, a mistake commonly made by some of the best artists a few years ago. When such great detail has to be shown, it is much better to use a wash drawing or a Ross board technique.

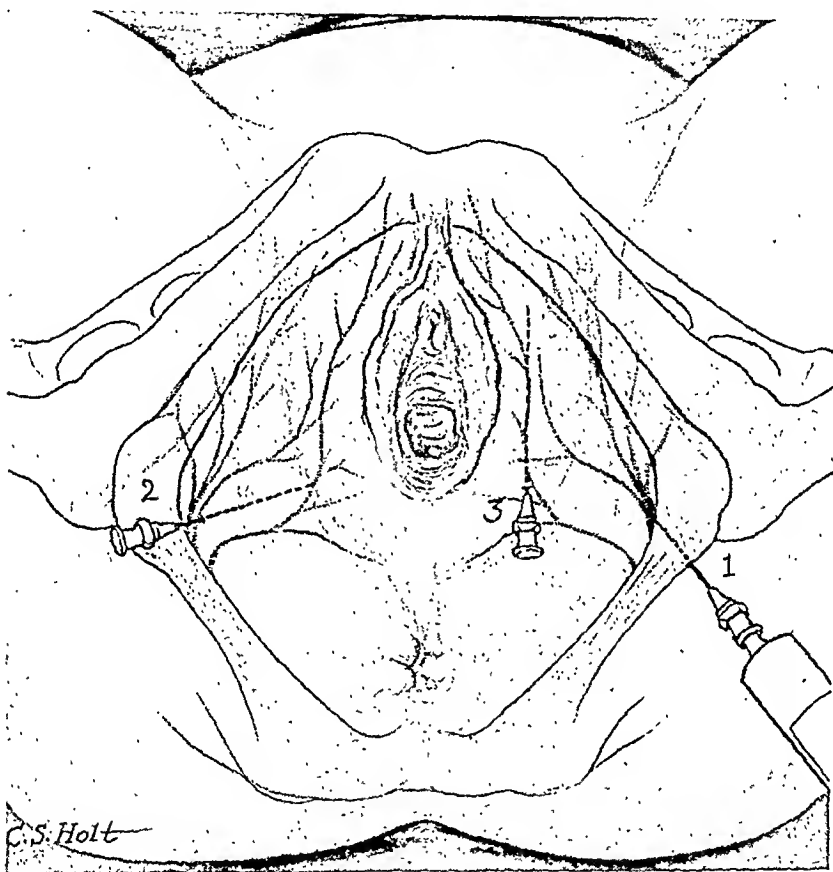
It is a good practice for the clinician to view the finished drawing through a reducing glass so that he may better visualize its appearance in the final publication before sending it to the publishers. Alterations can then conveniently be made if necessary.

While the simple black and white pen-and-ink drawing is very effective, it is frequently of considerable value to add color in the form of tinting to bring out some particular point to be emphasized. Under other

circumstances it may be advantageous to combine pen-and-ink and wash technique, and this can be done by an artist skilled in both methods with telling and pleasing effect.

It is also an important fact to be remembered that the reproduction of a pen-and-ink drawing for publication is only about one-half as expensive as that of a halftone. Another factor to be considered is that pen-and-ink reproductions can be printed on relatively low-grade and thin paper, whereas, halftone drawings and also colored plates must be

Local Anesthesia
Perineal block and infiltration



- 1, Blocking trunk of perineal nerve. 2, Blocking branches in urogenital septum.
3, Subcutaneous infiltration around vulval ring.

Fig. 3.—Combination of wash and pen-and-ink drawing by Charlotte S. Holt.

printed on a heavier book enamel stock which increases the size of a book appreciably when many illustrations are involved. The average printing establishment will turn out much better reproductions of pen-and-ink drawings than they will if halftones are submitted to them. However, first-class firms can handle either form of drawing equally well.

It may be pertinent to the discussion at this point to say that both the artist and author should demand proofs of all illustrations to go into an article or book, and should carefully proofread the same, noting defects and demanding good work. This of course can only be done when the originals supplied to the engraver are of good quality. It is surprising

how much better the finished article will appear if this simple precaution is taken. It is also true that most good publishers instead of resenting a request for illustration proofs appreciate the interest taken by the contributors.

The best all-around illustration, where utmost realism is desired, is the halftone. The clinician instinctively feels its usefulness and desirability, and usually requests it when other factors do not weigh too heavily in the balance. Its advantage is that it permits a wealth of detail and by skillful rendering of light and shade permits a realism which cannot be obtained in other forms of flat illustration. It can be done in black and white, and can be very beautifully combined with one or more colors. This technique can be used for publications or exhibit purposes, and lends itself well to photography, and can be reproduced beautifully

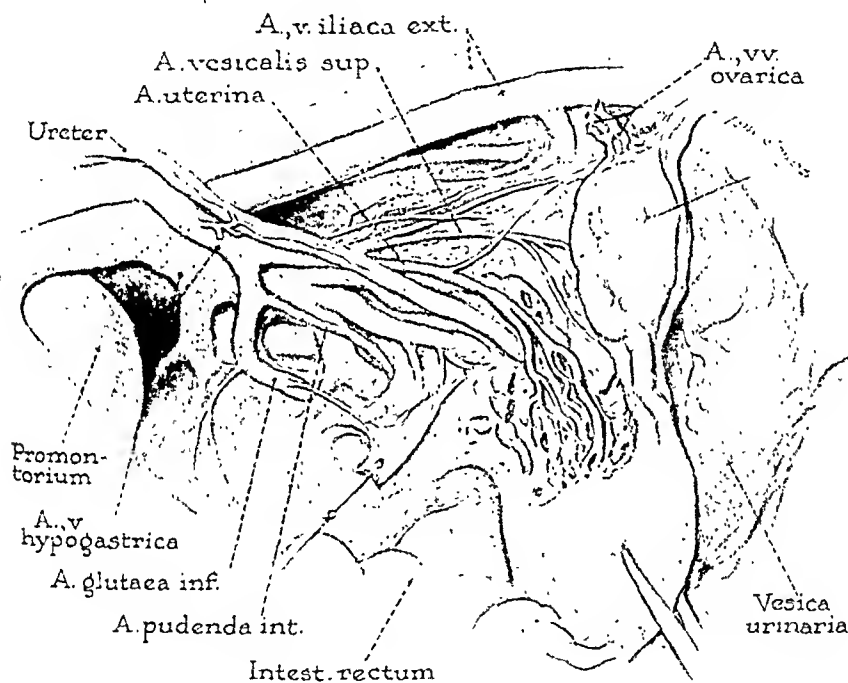


Fig. 4.—Example of wash technique by Tom S. Jones. (Curtis-Anson.)

in lantern slides. As mentioned above, it requires a somewhat heavier stock paper and is more expensive to reproduce properly than the pen and ink, and should not be submitted for reproduction to any except the best publishers. Within the last fifty years, Ross board technique has been used by some artists with very pleasing effect. This is a form of halftone illustration which depends upon obtaining shading, contrast and detail by use of a special Ross stipple paper and crayon dust. Max Brödel and his school have been the leading exponents of this method.

In the last few years a new approach has been developed in medical illustration by Dickinson and Belski in collaboration with Hoffman in New York, and Falls and Holt in Chicago. These workers have devoted themselves to making life-sized bas-relief models of obstetric subjects for exhibit and teaching purposes. Dickinson and Belski have depicted normal labor and the physiology of fertilization, while Falls and Holt have undertaken the reproduction of pathologic conditions, such as the

coats which vulcanizes in air at room temperature. A plaster back is next made over the rubber which is removed after setting. The rubber is then stripped off the clay model positive and placed in the plaster back to act as a negative. It is then filled with hydrocale (artificial marble) which sets, and when removed from the rubber mold can be painted realistically in oils giving a most striking effect. The use of latex permits of casting undercuts which would be quite impossible with any other material heretofore used. It has also the advantage

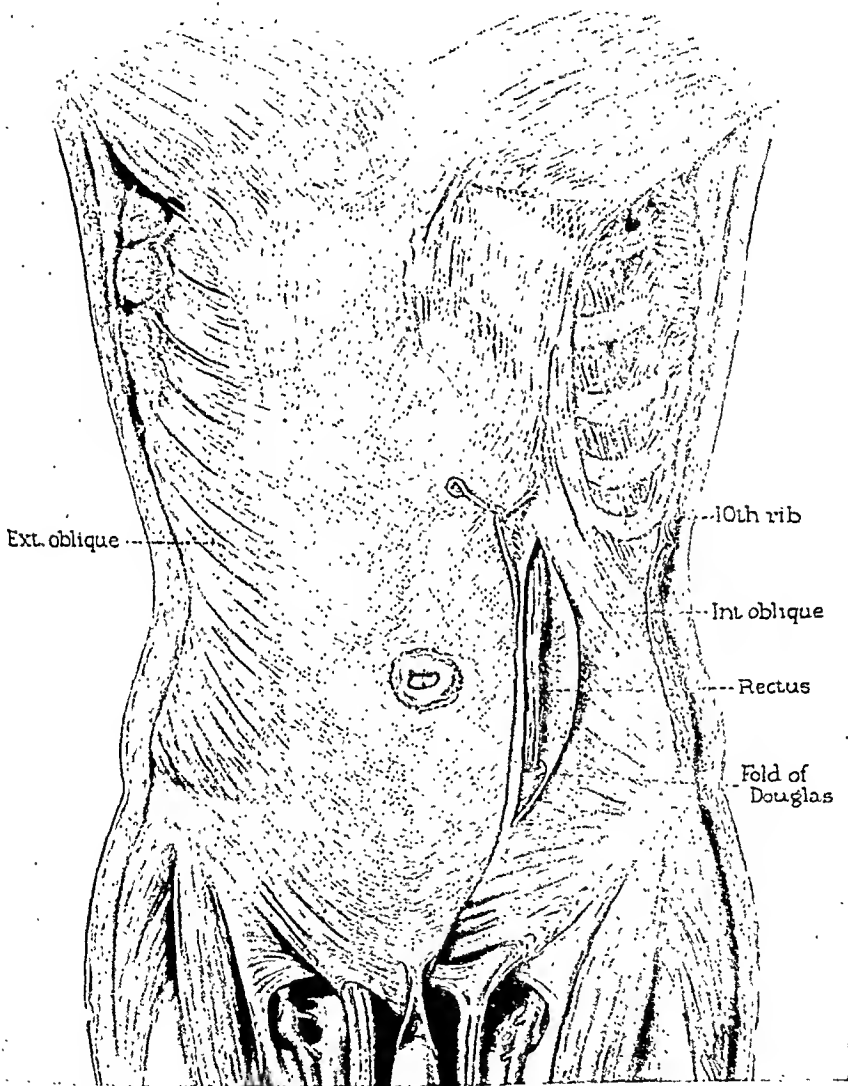


Fig. 6.—Ross board technique by Willard C. Shepard.

over most other materials used for making negatives, in that it can be used over and over instead of being destroyed by removal from the positive.

There is to my mind no doubt but that these models are the most valuable of all medical illustrative material for exhibit purposes because of the third dimension which produces a realism unattainable by other technique. When one adds life size and color painting, it leaves little to be desired.

The great drawback is the original cost of the materials for making the models, and for the time of the artist and clinician spent in making and remaking the sketches, clay models, and positives. However, the final product in artificial marble, which will outlast any other media, is worth the effort, especially since duplication by the method here indicated is comparatively inexpensive.

I have tried to outline in this address some of the factors which must be considered if satisfactory medical illustrations are to be produced. It is perfectly obvious to anyone who gives the matter more than casual consideration, that visual education is occupying more and more of the



Fig. 7.—Example of bas-relief model by Falls and Holt.

attention of medical teachers as well as those in other branches of education. Books without illustrations are almost a thing of the past. In many instances a book is judged more at least on cursory examination by the illustrations it contains than by the text.

It behooves us, therefore, if we are to keep abreast of the times, to consider carefully the type of illustration that will best suit the needs of a given publication, and to lend dignity and clearness to our presentations of medical contributions whether it be a lecture or published material, by providing appropriate drawings, slides, charts, or models. The desirability of pen and ink in one instance or a little color in another, a wash drawing here, a photograph properly posed and

illuminated there will give not only our audiences but also ourselves the highest degree of satisfaction.

Although much has been accomplished in recent years in this field, it is still a very young science. With the development of various forms of commercial art and the discovery and adaptation of new materials to old problems, the possibilities of finding new media to be used are enormous. It is for us a privilege to pioneer these new paths and to add our mite to the advancement of medical education.

The cost of medical illustration both for producing the illustration and in reproducing it in publications often may seem prohibitive, but if one considers the cost in time and effort on the part of the clinician to produce his part of the enterprise, and the permanent value of carefully done illustrative material, the outlay for the artistic side does not seem disproportionate.

Furthermore, it is remarkable how many different purposes a given drawing may fulfill. Thus we have made drawings of models to be used in an exhibit for medical men at the annual meeting of our State Society. These have been photographed and made into lantern slides which are used for undergraduate and postgraduate lectures to students, and to physicians who come to the University for short courses. Duplicate slides are sent out to County Medical Society meetings to illustrate postgraduate lectures. They are also used for nursing and even lay education when properly selected. Thus the use in many fields reduces the original cost very greatly.

Every educational institution offering medical courses should provide the members of its staff with facilities for good medical illustration if we are to advance in the field of medical education. I wish further to emphasize that it is not sufficient for trained artists and trained clinicians to attempt to produce good illustrative material at long distance. The artist must not only have the appreciation of his own field of work and technique, but he must also be given the clinical training necessary for him to appreciate the problem of presenting the ideas of the clinician to other physicians. It is, therefore, necessary for him to come in first-hand contact with the clinician and the patients, to see many operations on the subject under discussion, or to view first-hand fresh and preserved operative material so that he develops a knowledge of the fundamentals of the subject almost on a par with the physician. For this reason it is desirable and almost necessary for an artist in this field to have had considerable anatomy and some physiology and histology in his basic training.

For those of you who may be interested in art work, the time spent in assisting in the development of proper illustrations for your publications will soon be seen to be extremely valuable as a medium for clarifying in your own mind the essence of the subject material which you wish to present. It will necessitate an accuracy of detail which you would hardly have thought possible, and it will make you better medical men.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 13, 1942

The following paper was presented:

Clinical Experiments in Relation to the Excretion of the Estrogens. Dr. George van S. Smith (by invitation). (To be published in a later issue.)

MEETING OF FEBRUARY 10, 1942

The following papers were presented:

Tattooing With Mercuric Sulfide for Anogenital Pruritus. A Moving Picture Demonstration in Color. Dr. Robert Turrell (by invitation) and Dr. Samuel H. Geist.

Erythroblastosis Neonatorum. Dr. Carl T. Javert (by invitation). (For original article, see page 921.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 8, 1942

The following papers were presented:

A Report of 'Twenty-Seven Years' Work in Control of the Midwives of Philadelphia County. Dr. William R. Nicholson.

Preparation of Obstetricians and Gynecologists for War Emergencies. Dr. Hubley R. Owen.

End Results in the Treatment of Carcinoma of the Cervix. Lewis C. Scheffey, M.D., William J. Thudium, M.D., and David M. Farrell, M.D. (For original article, see page 941.)

Study of Maternal Deaths Due to Rheumatic Heart Disease. George L. Hoffman, Jr., M.D. (by invitation), and William Jeffers, M.D. (by invitation).

MEETING OF FEBRUARY 5, 1942

Devoted to a discussion of the Defense Program.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF NOVEMBER 18, 1941

The following paper was presented:

Studies in Renal Function in Normal Pregnancy and in Toxemia. Dr. Howard C. Taylor, Jr. (For original article, see page 567, April issue.)

MEETING OF JANUARY 20, 1942

The following study and case reports were presented:

Statistics on Cesarean Sections Throughout Massachusetts for 1940. Dr. Robert L. DeNormandie.

Delivery of a Double Headed Monster. Dr. Arthur F. G. Edgelow.

Bilateral Dermoid Cysts in the First Trimester of Pregnancy. Dr. Robert H. Goodwin.

Early Adenocanthoma of the Endometrium in a Twenty-Six-Year-Old Patient. Dr. Arthur T. Hertig and Dr. Paul A. Younge.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Pregnancy and Disease

Minniti, Giuseppe: Collapse Therapy by Pneumothorax in Tuberculous Pregnant Women With Special Attention to Labor and Puerperium, *Rassegna d'ostet. e ginec.* 48: 343, 1939.

The author reports upon 20 cases of pregnancy complicated by pulmonary tuberculosis. These patients were treated by means of collapse therapy during the course of their antenatal period and into the succeeding two months of the puerperium. All labors were normal. Low forceps applications were found necessary in but two of the deliveries. In no case was there evidence of exacerbation of the tuberculosis.

The author observed that artificial pneumothorax was compatible with the puerperal state. Except for unusual contraindications on the basis of more serious stages of the tuberculosis the disease can be treated by pneumothorax although the patient is pregnant.

The newborn infants of the mothers whose tuberculosis was treated throughout their pregnancies were found, as a rule, to be in even better states of nutrition than the infants borne by nontuberculous mothers of a similar age.

CLAIR E. FOLSOME.

Meixner, Fred M.: Pregnancy and Tuberculosis, *Illinois M. J.* 79: 482, 1941.

The author gives six principles to be considered in the tuberculous pregnant woman: (1) No one has shown definitely that pregnancy is good for the health of a tuberculous woman in any stage or type of tuberculosis. (2) At least 75 per cent of the investigators believe that pregnancy aggravates tuberculosis, while no one has proved that abortion, properly performed, aggravates an early quiescent or arrested lesion, if proper tuberculosis therapy is followed afterwards. In certain far-advanced cases, abortion may act as a stimulus to the chest lesion, and non-interference is preferable if it is felt that abortion will mean death for both mother and fetus; whereas the continuance of pregnancy may mean the death of the mother, thus sacrificing everything for a live child. (3) Pregnancy places a severe strain on a tuberculous woman's resources and strength, and labor is fraught with immediate and remote perils. (4) After abortion or labor, chest therapy must be continued until the pulmonary condition is arrested. (5) Future pregnancies should not be allowed until after careful study has shown complete arrest. (6) Therapeutic abortion, when decided upon, should be done as early as possible under spinal or evipal anesthesia. X-ray technique for therapeutic abortion has a distinct value in pregnant tuberculous women.

When a better and more intelligent understanding of the problem on the part of the tuberculosis specialist and the obstetrician is reached, the pregnant tuberculous

woman may emerge from her pregnancy experience almost, if not quite, as safely as the nontuberculous woman, but until that time has arrived therapeutic abortion is indicated before the fourth month of pregnancy.

EUGENE S. AUER.

Baker, Robert H., and Ward, Arthur D.: Pulmonary Tuberculosis and Pregnancy, New England J. Med. 226: 224, 1942.

The writers stress adequate and proper treatment of the tuberculosis during pregnancy which practically eliminates the necessity of therapeutic abortion. Under proper treatment, the associated pregnancy represents but little added risk. It is desirable to hospitalize these patients to secure care both of expert obstetricians and tuberculosis specialists.

Collapse therapy, preferably pneumothorax, should be instituted when possible and not discontinued during pregnancy. In active tuberculosis, this procedure is much more effective than abortion. After delivery vigorous therapy must be continued.

HUGO EHRENFEST.

Crabtree, E. G.: Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension, J. Urol. 44: 125, 1940.

A high percentage of pregnancy pyelonephritis cases show evidences of renal damage after five to eighteen years. Hypertension was present in 8 of 72 cases of pyelonephritis and in all of those that were complicated by toxemia. The relation of hypertension to the degree of renal damage was not always constant, but there was a closer relation of hypertension to the cases which showed marked renal insufficiency than to those which showed lesser degrees of damage to the kidneys. Hypertension is not the rule in cases of pyelonephritis pregnancy at from five to eighteen years after the infection.

J. P. GREENHILL.

Martius, H.: Etiologic Mechanism of Pyelitis of Pregnancy, Zentralbl. f. Gynäk. 65: 812, 1941.

Martius calls attention to the anatomic relationship between the colon and kidneys. Both kidneys have an area which is apposed to the colon, the one on the right being larger. The photographs of the dissected specimens and sketches of the free lymphatic connections between colon and kidneys at these points vividly suggest the possibilities for the transit of *B. coli* to the renal tissues. It is perhaps significant in this respect that the coli pyelitis is more common on the right, when the hypotonic and plethoric colon lies against the hypotonic and overloaded right kidney over a relatively large surface. The author suggests that in view of these findings more attention should be paid to emptying the colon in the management of acute pyelitis of pregnancy.

R. J. WEISSMAN.

Jaameri, E.: Infections of the Urinary Tract Associated With Pregnancy and Particularly Those Following Complications of Labor, Acta. obst. & gynec. Scandinav. 20: 306, 1940.

Under sterile precautions the author examined the urine of 600 pregnant or recently delivered women. He found organisms in the urine of 26.3 per cent. In this series 56 per cent were primiparas. Only 20 per cent of the women were aware of their infection and only 3 per cent of the healthy women complained of urinary

discomfort. Kidney disease seemed to be a predisposing factor in the etiology of infection of the urinary tract. Hyperemesis seemed to be a factor also. The author's study failed to ascribe to constipation any connection in the etiology of the urinary tract infections.

J. P. GREENHILL.

Heldfond, Alfred: *The Treatment of Urinary Tract Infection of Pregnancy*, West. J. Surg. 50: 82, 1942.

The author reports the results obtained with various chemotherapeutic agents in the treatment of 145 cases of pyelonephritis in pregnancy. In his hands sulfathiazole proved most effective.

HUGO EHRENFEST.

Tonker, E.: *Some Remarks on the Metabolism of the Carbohydrates in Pregnancy*, Monatschr. f. Geburtsh. u. Gynäk. 110: 313, 1940.

The author emphasizes that the carbohydrate metabolism is altered during pregnancy. It is, therefore, impossible to compare the blood sugar curves of pregnant diabetics with those of normal nonpregnant women. During pregnancy, there is an increased opportunity for acidosis and coma to develop.

Diabetes during pregnancy is a dangerous complication. Insulin has reduced the maternal mortality but has had little influence on the fetal death rate. The pregnant diabetic women run much more risk of developing toxemia than nondiabetic women.

The treatment of diabetes during gestation is by means of insulin. Over-development of the child can be prevented by keeping the maternal blood sugar low. Furthermore, labor must be shortened, otherwise acidosis might develop due to fasting and vomiting which often takes place. Likewise, narcosis should be avoided whenever possible. One should not hesitate too long before performing a cesarean section in the interest of the child.

J. P. GREENHILL.

Nothman, H.: *Diabetes Mellitus and Pregnancy*, New England J. Med. 224: 275, 1941.

Five diabetic women with a past history of several abortions and stillbirths were successfully delivered by prophylactic cesarean section. The high mortality rate of children of diabetic mothers may be decreased by this procedure. The influence that pregnancy will have on the diabetes of the mother cannot be predicted in any case, in spite of careful treatment. In the same patient, pregnancy at different times may take a very different course. A state of hypoglycemia in babies during the first days of life sometimes accompanied by periods of unconsciousness is described. The cause of this condition is the hypertrophy and over-function of the pancreas.

Considering the extremely high mortality rate of the fetuses and children of diabetic women, prophylactic cesarean section offers a favorable outlook. Therefore, this procedure is recommended to save the life of the endangered fetus.

J. P. GREENHILL.

Grott, J. W.: *Inflammation of the Pancreas During Pregnancy*, Monatschr. f. Geburtsh. u. Gynäk. 112: 77, 1941.

The author reports 12 cases of chronic inflammation of the pancreas discovered during pregnancy. From an analysis of these cases he insists that every woman in

whom glycosuria is discovered during pregnancy should have the pancreas examined, particularly during the puerperium. He describes a technique for manual examination of the pancreas.

J. P. GREENHILL.

Speiser, M. D.: Syphilis in the Pregnant Woman, New York State J. Med. 41: 240, 1941.

A special prenatal syphilis clinic was organized at Bellevue Hospital six years ago. In the last 16,437 deliveries, there were 790 patients diagnosed as having syphilis, an incidence of 4.8 per cent. In only 9 per cent was a history obtained of known syphilitic offspring who had either died as a result of their infection or were under treatment. Late abortions, premature deliveries, and term stillbirths occurred in 18.8 per cent of the cases, and in 24.7 per cent no significant data could be elicited in the history regarding a previous syphilitic infection.

The physical examination at the time of admission revealed early syphilitic lesions in 8.1 per cent of the patients and late lesions in 3.3 per cent. Therefore, 88.6 per cent of the patients with acquired syphilis were clinically latent. In the congenital group, manifestations were present in 65 per cent.

The value of serologic tests in establishing the diagnosis of syphilis is shown by the results of the tests in these cases. At Bellevue Hospital only the complement fixation test is employed.

While the effect of pregnancy upon syphilis offers a field for continued observation there is little doubt as to the disastrous effect of syphilis upon pregnancy. There were 95 untreated mothers who delivered 97 babies, and premature termination occurred in 51.5 per cent of the cases. In 81.5 per cent there were deaths due to syphilis or liveborn babies with syphilis, while only 13.4 per cent were free from the disease. Faulty presentation occurred in 12.4 per cent. In patients with early lesions who had received no treatment, 54 per cent had a morbid post-partum course. In the entire untreated group, the morbidity was 23.1 per cent.

A total of 566 cases were studied from the standpoint of the effect of syphilis upon pregnancy and the value of treatment. There were 517 babies delivered of 512 mothers who had acquired syphilis. Treatment given only during pregnancy salvaged 61.9 per cent of the babies, while treatment given both before and during pregnancy saved 92.1 per cent of the babies. A disastrous result in the latter group occurred in only 4.1 per cent, while in the former group it occurred in 25 per cent. Where treatment was started any time after the sixteenth week of gestation even in the absence of previous therapy, the incidence of prematurity was reduced to 14 per cent, disastrous results occurred in 29.5 per cent and 55.6 per cent were free of the disease.

The treatment of the syphilitic prenatal patient depends upon the absence of medical and obstetric contraindications, the stage of the syphilitic process, the length of gestation, and the tolerance for the drugs employed. A definite conclusion as to the status of the newborn child often cannot be reached before it is discharged from the hospital. Treatment should be withheld until a definite diagnosis is established.

J. P. GREENHILL.

Smith, Frank R., Jr., and Spence, John M., Jr.: Congenital Syphilis in Only One of Twins, South. M. J. 34: 147, 1941.

Of the 12 individual case reports dealing with this interesting condition which the authors encountered in a survey of the available medical literature, they considered only five completely acceptable because they possessed the essential criteria for this

diagnosis. These requirements are: (1) The congenital nature of the infection in the syphilitic twin must be clearly proved, and (2) the fact must be established beyond peradventure that the apparently non-syphilitic twin neither has had syphilis in the past nor is in the process of developing the disease.

Their own experience is based upon two cases personally observed. To the abstracts of these histories they have added two additional ones obtained from the records of the Johns Hopkins Hospital; the history of a fifth instance of this condition was supplied by a colleague. The fact that 4 of these 5 cases occurred among 44 twin gestations in 40 women with syphilis indicates that this anomalous phenomenon is not so rare as might be expected.

There are numerous hypotheses and theories, but no factual explanation for the occurrence of this condition. Of great significance is the fact that in the 5 cases reported all the twins were binovular. The authors conclude that, "the operation of sheer chance probably provides the best explanation."

ARNOLD GOLDBERGER.

Mankin, Z. W.: The Effect of Pregnancy and the Puerperal State on the Growth of Malignant Tumors, *Arch. f. klin. Chir.* 199: 337, 1940.

A careful analysis of clinical developments in a considerable series of cases in which a pregnancy was complicated with a malignant growth somewhere in the body leads the author to the conclusion that the pregnancy by itself does not accelerate the growth of the malignant tumor, but that the deleterious effect follows labor, abortion, puerperium, and lactation. This holds true for cancers in the breast, uterus, intestinal tract, etc. Therefore nothing is gained by interruption of the intercurrent pregnancy, and as a matter of fact continuation of gestation to term often affords valuable time to deal with the malignancy before the puerperal or postabortal stage begins its inevitable aggravating effect.

HUGO EHRENFEST.

Brendler, F.: Conception and Spontaneous Childbirth With Previous Diagnosis of Carcinoma of the Cervix, *Zentralbl. f. Gynäk.* 64: 1464, 1940.

The author discusses the confused state of knowledge of the effect of pregnancy upon the activity of uterine carcinoma. An interesting case is presented: A 42-year-old para ii was in good health until 1935 (aged 37), when she first experienced vaginal discharge and irregular bleeding. A suspected erosion was excised by her physician and on microscopic study was found to be a squamous cell carcinoma deeply infiltrating the tissues, but without outstanding cornification. In the stroma many secondary nests of cells were found. The patient refused further operation as she was now free of symptoms. Six months later she missed her first period and the following month a diagnosis of pregnancy was made. There were no symptoms of recurrence of the growth and nothing could be found on examination. Sudden bleeding and a rapid spontaneous delivery occurred during the eighth month of pregnancy. The woman was examined twice not long post partum and nothing abnormal was found.

Two years later irregular bleeding occurred, and after two months the patient appeared for examination which revealed a moderately sized exophytic tumor growing out of the cervix with a central crater admitting 1 finger. The growth was strictly confined to the portio. The parametrium appeared stiffened but not infiltrated. Histologically: squamous cell carcinoma with strong inflammatory reaction. Radium roentgen therapy was administered, and four months later on return for another treatment the vagina was found to be now a blind pouch. The left parametrium appeared stiffer than the right. There was no apparent recurrence and the patient

had gained $2\frac{1}{2}$ kilos. At three-month intervals, until the writing of the report, no recurrence was found. The author feels that pregnancy is inimical to the activity of early carcinoma but that this may not be the case in pregnancy associated with well-established malignant growths.

R. J. WEISSMAN.

Putz, T.: The Healing of Fractures During Pregnancy and the Course of Labor After Fractures of the Pelvis, Monatschr. f. Geburtsh. u. Gynäk. 112: 17, 1941.

Three cases of fracture of the pelvis were observed by Putz at the Essen clinic. In the first case the patient was five months pregnant at the time of the fracture. She was able to walk four and one-half weeks after the accident occurred. Labor and the puerperium were uneventful. In the second case a severe fracture of the right thigh occurred during the eighth month of pregnancy. With the aid of Kirshner's wire extension, healing promptly followed. The third case of fracture of the pelvis was an old fracture in which the symphysis pubis had an opening, the breadth of a hand. In spite of this the patient had no difficulty in walking. Labor and the puerperium were uncomplicated.

The author points out that in spite of the favorable results in these three cases, fracture of the pelvis should not be considered lightly. In the literature there are cases where, following fracture of the pelvis, disturbances occurred, such as stillbirths and difficult forceps deliveries. Careful clinical x-ray examinations must determine whether the fractures result in hindrance to vaginal delivery or whether cesarean section is indicated.

J. P. GREENHILL.

Dyer, I.: Measles Complicating Pregnancy, South. M. J. 33: 601, 1940.

From an experience based upon the observation of 24 cases of measles complicating pregnancy, the author concludes that the coincidence of the two conditions is probably greater than the literature indicates; also, that the effect upon the pregnancy is not serious. These cases occurred in a rather widespread epidemic during the winter months in a rural community.

Provided that the mother has had the disease at least several months before delivery, the infant is protected from measles by an absolute immunity up to the fifth month, and by relative immunity up to the eighth month. Whereas there was no effect upon the pregnancy in 15 of these 24 cases, uterine contractions occurred in 11 cases. These were most frequently noted near the end of the period of incubation and on the first day of the eruption. In 9 patients termination of the pregnancy was attributed to the disease. Of these, 6 had reached or passed the thirty-eighth week of gestation, 2 were premature at thirty-three weeks and one aborted at eighteen weeks. Three infants had congenital measles; one of them contracted pneumonia at one month of age and died. A cesarean section was performed at the height of the exanthem and the infant was born with an extensive rash and Koplik's spots. Uneventful recovery occurred.

There was no maternal mortality, and in the one instance of morbidity a low-grade fever developed three weeks after the measles.

ARNOLD GOLDBERGER.

Mayr, Julius: The Question of Interruption of Pregnancy in Cases of Herpes Gestationis, München. med. Wchnschr. 87: 742, 1940.

Mayr discusses the symptomatology of herpes gestationis, and reports 6 cases. He states that the usual therapy, which consists of calcium, serum from normal pregnant

women, parathyroid hormone, sedatives and hypnotics, has no special value. The herpes may affect primiparas and multiparas, may appear at any time during pregnancy, although the prognosis seems to be worse the earlier in pregnancy the herpes appears. It has to be differentiated from impetigo herpetiformis, another pregnancy toxicosis which previously was considered serious enough to justify an interruption. But impetigo is due to a disturbance in the calcium metabolism and can now be completely cured with parathyroid hormone. In fact the success of the parathyroid hormone therapy aids in the differential diagnosis.

He concludes that the only therapy today for the severe cases of herpes gestationis is interruption of pregnancy and that the physician should not hesitate to undertake this procedure.

C. E. PROSHEK.

Kraines, S. H.: *The Treatment of Psychiatric States Following Pregnancy*, Illinois M. J. 80: 200, 1941.

The author states that the incidence of puerperal psychoses among female admissions to mental institutions is from 5 to 10 per cent of all cases, and because general population psychoses occur in about the same proportion as puerperal psychoses, the inference can be drawn that pregnancy is the precipitating and not the causative factor in puerperal psychosis. In other words one may say that each person who develops a post-partum psychosis is psychotically predisposed.

The number of pregnancies which a patient has experienced does not seem to be significant. There are three common forms of the disease: (1) toxic; (2) schizophrenic; and (3) manic-depressive. The prepsychotic personality of these patients determines the form of their illness. Schizophrenic reactions are to be found most frequently in those persons whose pre-psychotic personality could be described as "introvert"; manic-depressive, in those whose tendency was to be "extrovert."

The treatment of psychiatric states following pregnancy is divided into three main categories. The first is the removal of toxic-infectious processes where they are discernible by the usual medical treatment. The clearing up of the infectious process will usually result in complete recovery of the toxic type of psychosis. The second form of treatment is convulsive shock treatment with either metrazol or electricity. The third form of therapy is psychotherapy which is directed toward the removal of the instability that exists in relation to the post-partum disturbance and the prevention of further neurotic disturbances. In those patients where the menstrual period is associated with emotional disturbance, testosterone propionate has been found useful.

EUGENE S. AUER.

Wick, Samuel: *Puerperal Psychoses*, Wisconsin M. J. 40: 299, 1941.

Within 6 months seven patients were admitted to the Milwaukee County Hospital for Mental Diseases who had psychoses associated with the puerperium.

There were four with dementia precox, and three with manic-depressive psychosis of which one was depressed.

In 6 of the patients the first attack of mental illness was associated with pregnancy. It would seem likely that these women would not have had a mental illness if they had not been subjected to additional strain, both physical and psychic, incident to pregnancy. Unfortunately there are no definite signs to indicate which women should be advised against childbearing. Four of the patients in the series recovered and of the 3 who are unimproved, one has been ill four years, one for one year, and the third had a previous attack from which she recovered. The average duration of the psychosis in those who recovered was four months.

The treatment varies, depending on the symptoms which are present. In general these patients can be aided by early hospitalization where nutrition and fluids are maintained, elimination is increased, restlessness diminished, and exhaustion avoided. Insulin and metrazol therapy have been employed with the same results as in other cases of schizophrenia.

J. P. GREENHILL.

Schwaighofer, G.: Adrenal Insufficiency With Grippe in Pregnancy, *Zentralbl. f. Gynäk.* 64: 1719, 1940.

Sudden and unexpected deaths occur in pregnant women contracting grippe. The author feels that the generalized swelling and hyperemia of the mucous membranes of the gravid woman allow easy permeation of bacteria and toxins. This, however, does not explain the sudden deaths in many cases. A 26-year-old gravida ii in the last month of pregnancy contracted influenza with bronchopneumonia. On the third day of her illness she suffered a peripheral vascular collapse with cold skin, empty veins, tachycardia, and tachypnea. There was no edema and no special findings were noted in heart or lungs. The fetal heart could not be heard. When the patient suddenly died, an immediate abdominal incision was made and a dead slightly macerated fetus was removed. At autopsy the lungs showed solely a hemorrhagic bronchitis; the heart was normal. Liver and kidneys showed cloudy swelling microscopically. Both adrenals, however, were enlarged and had hemorrhagic infarcts. In the right adrenal vein, a fresh dark red thrombus was found. The appearance was typical of adrenal apoplexy. Apparently as a result of parenchymal changes in infections, hyalin thrombosis takes place in venous capillaries, extending to the adrenal veins. Changes observed in the adrenal cortex are diminution and disappearance of lipid droplets followed by vacuolation in the plasma with degeneration of cell nuclei. Congestion, hyperemia, edema of the gland and infarction follow. With the suspension of adrenal cortex function adynamia and other symptoms follow rapidly.

R. J. WEISSMAN.

Acciavile, Dario: A Case of Acute Torsion of the Pregnant Uterus, *Ginecologia* 19: 199, 1941.

The author describes a case of acute torsion of a pregnant uterus. The patient was 24 years of age and about three months pregnant. The torsion was complicated by a chronic appendicitis which had re-exacerbated to the subacute stage.

Laparotomy revealed the uterus to be rotated upon its isthmus a full 180 degrees from the left to the right. The left adnexal area was adherent to the ileoceco-appendicular region. The left adnexal adhesions were freed, the pregnant uterus restored to its anatomic axis and the right adnexal tissue was removed with the offending appendix. The patient was confined by a normal delivery at term.

CLAIR E. FOLSOME.

Bowles, H. E.: Bilateral Ovarian Dermoid Cysts Complicating Pregnancy, *West. J. Surg.* 50: 78, 1942.

To the so far reported 47 instances of the complication of pregnancy with bilateral ovarian dermoids Dr. Bowles adds five new observations, including one tubal pregnancy.

He believes that the optimum time for operation is the fourth month of gestation when placental hormones become active. Surgery should be done earlier only in the

presence of urgent symptoms suggestive of torsion, hemorrhage, etc. If the diagnosis is made only late in pregnancy, interference should be delayed until after viability, and then cesarean section done.

HUGO EHRENFEST.

Hoff, Franz: Torsion of the Ovary in Pregnancy, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 48, 1940.

A patient is described who, in about the thirty-fifth week of her fifth pregnancy, suddenly developed severe cramplike pain in the right lower abdomen. At operation an infarcted right ovary was found and removed. On the eighth day after operation she went into labor and was rapidly (thirty-three minutes) delivered of a normal living female child. The placenta failed to separate and was manually removed six hours after delivery. Mother and child had an uncomplicated subsequent course.

The literature dealing with torsion of tube, ovary, and both is discussed. The various theories of the etiology of the condition are critically examined. The author concludes that it arises as a result of a combination of various "predisposing factors" with other factors (Realisationsfaktoren) which produce the torsion when conditions are favorable. The most important predisposing factor is a congenitally elongated ovarian ligament. When this is present, mechanical factors tending to rotation and a hemodynamic factor (hyperemia, vascular obstruction) may act together to produce the torsion. It is the author's opinion that one of these alone is not sufficient.

The reported cases are listed in tabular form. The prognosis is good if the condition be recognized and surgical treatment quickly instituted.

J. L. MCKELNEY.

Kisimoto, Okai, and Torihudi: Intraabdominal Hemorrhage From Spontaneous Rupture of a Subserous Blood Vessel of the Uterus During Pregnancy, *Japanese J. Obst. & Gynec.* 23: 238, 1940.

The authors report a case of a patient who was admitted to the hospital in the last month of pregnancy with a diagnosis of abruptio placentae. However, at operation it was found that the patient had a twin pregnancy with severe hemorrhage from a ruptured subserous blood vessel of the uterus. A supravaginal hysterectomy was performed. The patient recovered.

In the literature there are only 11 similar cases. In all of the cases the hemorrhage occurred spontaneously and the site of rupture was the posterior wall of the uterus. The most likely cause of the rupture of the blood vessel was friability of the wall of the vein involved. Overdistention of the uterine wall and other mechanical factors may play a role.

In not a single case of the literature was the correct preoperative diagnosis made. Prognosis is very bad; 8 of the 11 patients reported in the literature died. Furthermore, in most of the cases, the babies also perished. In the authors' case, the babies were dead before the operation was performed.

The treatment may consist of suture of the ruptured vessel followed by cesarean section, but often a Porro operation must be done.

J. P. GREENHILL.

Items

Continuation Courses in Gynecology and Obstetrics for Practicing Physicians

INSTITUTION	COURSE BEGINS	LENGTH AND CONTENT OF COURSE	NO. OF STUDENTS ACCEPTED	REGISTRATION FEE AND/OR TUITION	FOR DETAILED INFORMATION WRITE TO
Gynecology					
Columbia University, including the New York Post-Graduate Medical School	Enter first Monday of any month when a vacancy occurs	15 sessions, MWF mornings or afternoons; Cystoscopy and Endoscopy	6	\$75s	The Director, Columbia University School of Medicine, 309 East 20th Street, New York City
	Monthly	10 sessions, 3 mornings or afternoons a week; Diagnosis and Office Treatment	6	\$40s	
	Monthly	15 sessions, MWF afternoons; Diagnosis and Office Treatment	6	\$60s	
	Enter first Monday of any month when a vacancy occurs	24 sessions, TTS mornings; Gynecologic Endocrinology	42	\$100s	
	Arranged on application	4 or more hours weekly for 4 weeks or longer; Gynecologic Pathology		Arrangeds	
	Arranged on application	12 sessions, TTS mornings, for 4 weeks; Surgical Anatomy as Applied to Operative Gynecology (cadaver)	2-34	\$200s	Dr. Frank R. Ober, Dean, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts
Harvard Medical School, Courses for Graduates	June, July	Mornings for 1 month	4 per mo. ¹	\$75	
	Monthly	10 sessions, 2 mornings and evenings a week; Gonorrhea in Women	3	\$20	

Obstetrics

Columbia University, including the New York Post-Graduate Medical School	First of any month from Jan. to Oct.	Full time for 3 mo.; Internship Training		\$350	The Director, Columbia University School of Medicine, 309 East 20th Street, New York City
Duke Medical School and Hospital	First of any month	1 month; Observation Course		\$100	Dr. G. M. Cooper, North Carolina State Board of Health, Raleigh, North Carolina
Harvard Medical School, Monthly Courses for Graduates	Arranged on application through July 1 or later	5 days; Obstetrics and Pediatrics	4-6 ²⁰	None ²¹	Dr. Frank R. Ober, Asst. Dean, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts
Indiana University, School of Medicine	Monthly	1 month or more; Clinical Obstetrics	8 ¹	\$125	Dr. C. J. Clark, Chairman, Indiana University School of Medicine, Indianapolis, Indiana
Louisiana University Medical Center	Arranged on application	Arranged	10	\$10	Dr. C. P. Huber, Director, Post-Graduate Course in Obstetrics, Indiana State Board of Health, 1098 West Michigan Street, Indianapolis, Indiana
University of Nebraska, College of Medicine	July 13	Full time, 2 weeks; Obstetrics and Gynecology	6 ²	\$10 ²¹ , 22	Dr. V. E. Webb, Chief, Division of Maternal and Child Health, Louisiana Department of Health, New Orleans, La.
	June 1	2 weeks; intensive refresher course	Limited ²³	None ²¹	Dr. C. W. M. Poynter, Dean, 42 Street and Dewey Avenue, Omaha, Nebraska

¹Male physicians only.²Physicians with adequate preliminary training and/or approved by the postgraduate department are eligible.³Limited to specialists who have had preliminary training and experience.⁴Upon application by physicians otherwise unable to meet the expense of postgraduate study, grants to defray part of the tuition are made from a scholarship fund.⁵For state physicians. Some out-of-state physicians accepted.⁶State boards of health furnish funds covering tuition fees, maintenance, or transportation for physicians of the state.⁷All or part refunded on satisfactory completion of the course.

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Atlantic City, N. J., by the entire Board, from Thursday, June 4, through Tuesday, June 9, 1942, prior to the opening of the annual meeting of the American Medical Association.

Group A, Part II, candidates will be scheduled for examination the first part of the examination period, and Group B, Part II, the latter half. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

DISEASES OF METABOLISM. Detailed Methods of Diagnosis and Treatment. Edited by Garfield G. Duncan, M.D., Chief of Medical Service "B," Pennsylvania Hospital, Associate Professor of Medicine, Jefferson Medical College, Philadelphia, Pa. 158 illustrations and 7 plates in color, 985 pages. W. B. Saunders Company, Philadelphia, Pa., 1942.

INTERNAL MEDICINE IN OLD AGE. By Albert Mueller-Deham, M.D., Associate Visiting Physician, Welfare Hospital for Chronic Disease, etc., and S. Milton Rabson, M.D., Assistant Professor of Pathology, New York Post-Graduate Medical School, Columbia University, etc. 396 pages. The Williams & Wilkins Company, Baltimore, 1942.

THE BOND BETWEEN US. The Third Component. By Frederic Loomis, M.D. 267 pages. Alfred A. Knopf, New York, 1942.

THE HISTORY AND EVOLUTION OF SURGICAL INSTRUMENTS. By Dr. C. J. S. Thompson, with a foreword by Dr. Chauncey D. Leake. 115 illustrations, 113 pages. Schuman's, New York, 1942.

PEDIATRIC GYNECOLOGY. By Goodrich C. Schauffler, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School, etc. 65 illustrations, 384 pages. The Year Book Publishers, Inc., Chicago, 1942.

UROLOGICAL DISEASES OF PREGNANCY. By E. Granville Crabtree, M.D., Urologist to the Boston Lying-in Hospital. With a chapter by George C. Prather, M.D., Assistant Urologist to the Boston Lying-in Hospital. 158 illustrations, many in color, 472 pages. Little, Brown and Company, Boston, 1942.

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TABLE II. ARITHMETIC MEANS AND STANDARD DEVIATIONS

	CONTRACTION PHASE		RELAXATION PHASE		OVER-ALL DURATION		DISPLACEMENT		FREQUENCY PER HOUR	
	\bar{X}	σ	\bar{X}	σ	\bar{X}	σ	\bar{X}	σ	\bar{X}	σ
(A) Combined unselected multiparas and primiparas	66.38	32.33	88.48	43.64	154.86	60.28	0.98	0.54	17.5	8.96
(B) Unselected multiparas. Gr. ii to xviii	67.80	32.03	91.19	46.90	158.99	63.07				
(C) Selected multiparas. Gr. ii to xviii	69.57	28.42	91.07	50.12	161.24	69.04				
(D) Selected multiparas. Gr. ii to vi	65.45	23.90	86.37	42.39	151.82	51.64	1.03	0.57	16.3	8.70
(E) Unselected multiparas with premature ruptured membranes. Gr. ii to xviii	64.42	28.13	82.24	39.70	146.66	54.81				
(F) Select multiparas with premature ruptured membranes. Gr. ii to vi	64.86	28.16	83.60	40.96	148.46	54.51				
(G) Unselected primiparas	64.96	31.80	86.76	37.90	151.72	55.78				
(H) Selected primiparas	60.09	25.71	80.16	31.31	140.25	47.56	0.96	0.50	18.5	8.90
(I) Unselected primiparas with premature ruptured membranes	68.72	37.58	84.02	41.32	152.74	59.21				
(J) Selected primiparas with premature ruptured membranes	67.29	41.44	84.75	32.83	152.04	46.80				

TABLE III

	SIGNIFICANCE RATIOS			
	DISPLACEMENT	CONTRACTION PHASE	RELAXATION PHASE	OVER-ALL DURATION
(A) Combined unselected multiparas and unselected primiparas versus unselected multiparas, Gr. ii to xviii	0.65	2.07	1.80	3.16
(B) Unselected multiparas, Gr. ii to xviii versus select multiparas, Gr. ii to xviii		1.17	0.19	0.25
(C) Unselected multiparas, Gr. ii to xviii versus select multiparas, Gr. ii to vi		1.65	1.96	5.13
(D) Unselected multiparas, Gr. ii to xviii versus unselected multiparas with premature rupture of membranes		2.87	3.75	4.87
(E) Select multiparas, Gr. ii to vi versus select multiparas with premature rupture of membranes		0.29	0.89	1.03
(F) Combined unselected multiparas and unselected primiparas versus unselected primiparas	0.97	1.49	2.48	3.16
(G) Unselected primiparas versus select primiparas		2.87	3.87	3.03
(H) Unselected primiparas versus unselected primiparas with premature rupture of membranes		2.82	1.46	4.00
(I) Selected primiparas versus selected primiparas with premature rupture of membranes		3.49	1.48	0.75
(J) Selected primiparas with premature rupture of membranes versus selected multiparas with premature rupture of membranes		1.22	0.35	0.86
(K) Unselected multiparas versus unselected primiparas	2.45	3.01	3.66	5.89
(L) Select multiparas, Gr. ii to vi versus select primiparas		2.65	2.10	0.65
(M) Select multiparas with premature rupture of membranes, Gr. ii to vi versus select primiparas with premature rupture of membranes		1.22	0.35	0.86
				2.61
				1.58
				1.42
				1.42

select group relative to the contraction phase, no improvement in the relaxation phase or the over-all duration; in fact, the standard deviation from the mean is increased with ease selection.

Difficulty was initially experienced in accounting for these results. Investigation disclosed that many of the extremes found in the tabulated data for the selected multiparas were associated with multiparas, gravida vi to xviii. It was deemed advisable to exclude the findings of these cases from the class of selected multiparas. Analysis of the selected multiparas, gravida ii to vi, gave the following results (Table II, B versus D). Improvements in the standard deviations are present in the selected cases in regard to the contraction, relaxation phases and the over-all duration of the contractions. At the same time there occurs a general decrease in the arithmetical means. Inspection of the respective significance ratios (Table III, C) shows a significant decrease in the over-all duration while a possibility exists that the decrease in contraction and relaxation phases may exist. In general, the findings show tendencies similar to those observed in the primiparas.

The results obtained from the selected primiparas were compared with those obtained from the selected multiparas, gravida ii to vi (Table II, H versus D and Table III, L). The means for the contraction phase, relaxation phase and over-all duration are larger for the multiparas. The standard deviation for the relaxation phase and over-all duration are less for the primiparas than for the multiparas. No significant difference exists between the means of the over-all duration of contractions, but there exists a possibility that a significant difference exists between the relaxation phases and a probability that a statistically significant difference exists in the contraction phases.

In view of the number of primiparas and multiparas with prematurely ruptured membranes, it was deemed advisable to study these cases separately to determine their deviation from the "normal." In addition all the cases were analyzed in terms of duration of labor, time of rupture of the membranes compared to time of delivery, and duration of time between rupture of membranes and the onset of clinical labor. The following represent the means of each group.

Primiparas with early, usual or delayed rupture of membranes:

Clinical labor duration	17.0 hours
Rupture of membranes	4.3 hours before delivery
Interval between onset of labor and rupture of membranes	12.0 hours

Primiparas with premature rupture of membranes:

Clinical labor duration	16.6 hours
Rupture of membranes	23.6 hours before delivery
Interval between rupture of membranes and onset of labor	7.4 hours

Multiparas with early, usual or delayed rupture of membranes:

Clinical labor duration	11.5 hours
Rupture of membranes	3.4 hours before delivery
Interval between onset of labor and rupture of membranes	7.9 hours

Multiparas with premature rupture of membranes:

Clinical labor duration	6.6 hours
Rupture of membranes	27.4 hours before delivery
Interval between rupture of membranes and onset of labor	20.8 hours

From the above, the average duration of clinical labor for all primiparas was 16 plus hours; for all multiparas 9 plus hours. In the multiparas and primiparas with usual, early or delayed rupture of membranes, the average times for rupture of membranes before delivery were comparable (4.3 hr. and 3.4 hr.) with a mean of 3.85 hours. In the multiparas and primiparas with spontaneous premature rupture of membranes, the average times for rupture of membranes before delivery were comparable (23.6 hr. and 27.4 hr.) with a mean of 25.5 hours for the two classes. In primiparas with prematurely ruptured membranes, the average duration of clinical labor was 16.6 hours, a value comparing favorably with the average of seventeen hours for primiparas with unruptured membranes. In multiparas with spontaneous premature rupture of the membranes, the average duration of clinical labor was 6.6 hours which is considerably less than the average duration of clinical labor for multiparas (11.5 hours) with intact membranes. For primiparas, the average interval of latency between spontaneous rupture of membranes and the onset of clinical labor was 7.4 hours; whereas for multiparas it was 20.8 hours. This difference can be accounted for by the fact that there were in the multipara series 16 patients who were not at term and one of which had a latency of 356 hours. When the multiparas were limited to those patients of thirty-eight to forty-two weeks' pregnancy, the latency was found to be 12.5 hours. While those multiparas between twenty-eight and thirty-seven weeks of pregnancy had an average latency of 38.6 hours.

The contractions of multiparas with spontaneous premature rupture of membranes were analyzed separately in respect to the contraction, relaxation phases, and the over-all duration of the contractions. Findings in terms of arithmetical means and standard deviations are shown in Table II (E). Table III (D) shows the statistical ratios found when comparisons were made between the findings of the unselected multiparas with intact membranes and the unselected multiparas with ruptured membranes. The means of the contraction phase and relaxation phase and durations are larger for the multiparas with ruptured membranes, significantly so for duration and relaxation phase, and probably so for the contraction phase. On the other hand the findings in regard to the arithmetical means and standard deviations for selected multiparas (gravida ii to vi, with premature rupture of membranes) (Table II, F), do not differ significantly when compared to findings of the selected multiparas with unruptured membranes (Table III, E).

The contractions of the primiparas with spontaneous premature rupture of membranes were analyzed separately in respect to the con-

traction, relaxation phases, and over-all duration of the contractions. The results in terms of arithmetical means and standard deviations are shown in Table II (I). The statistical comparison of this class with corresponding unselected cases is shown by the ratios found in Table III (H). It is seen that the means of the over-all durations are increased, and on closer inspection the contraction phase plays the more prominent role in the increase. When the primiparas were selected according to the standards set up, the findings in terms of the mean and standard deviations are shown in Table II (J). These findings when statistically compared with selected primiparas (Table II, H), show the statistical ratios found in Table III (I). A significant difference exists only in the duration of the contraction phase. The selected primiparas with premature rupture of membranes when compared with selected multiparas with premature rupture of the membranes show no difference of statistical significance (Table III, J).

The duration of the contraction phase was statistically compared with the duration of the relaxation phase throughout all classes or groups of patients. Table II indicates that without exception the duration of the relaxation phases is significantly longer than the duration of the contraction phase. Table IV of significant ratios indicates that the chances are exceedingly remote that in any similar series of cases that the reverse would be true.

The over-all duration of the unselected small contractions secured from all sources were subjected to statistical analysis. The arithmetical mean was found to be 59.3 seconds and the standard deviation was 17.9 seconds.

Analysis was made of all the recordings in terms of frequency of large contractions per hour. Table II (A, B, and G) show the arithmetical means and standard deviations. The average frequency of large

TABLE IV

	SIGNIFICANCE RATIOS ASCENT VS DESCENT
Combine unselected multiparas and unselected primiparas	9.68
Unselected multiparas gravida ii to xviii	21.12
Selected multiparas gravida ii to xviii	8.00
Selected multiparas gravida ii to vi	8.02
Unselected multiparas with premature rupture of membranes	10.20
Selected multiparas with premature rupture of membranes	7.32
Unselected primiparas	20.66
Selected primiparas	8.24
Unselected primiparas with premature rupture of membranes	6.67
Selected primiparas with premature rupture of membranes	6.22

contractions was 17.5 per hour. No statistically significant difference in this connection was found to exist between the primiparas as a group and the multiparas as a group (Table III, A, F, and K).

Furthermore all recordings were analyzed in respect to the plus or minus percentage of spontaneous change in frequency response. In

selected patients in which individual recordings used were obtained fifteen hours or less before delivery and compared with those secured one or less hours before or after any individual recording, the mean plus or minus spontaneous change was found to be 27 per cent with a standard deviation of 15 per cent.

DISCUSSION

The recorders used in this investigation measure surface displacements; it is readily understood that topographic changes of the anterior abdominal wall are recorded. Our analysis shows that the displacements associated with uterine contractions are the result of the single or combined action of three uterine factors:

1. The change which occurs in the cross-sectional outline of the uterus with the rise in internal tension. This change is characteristic in that a fluid-filled organ having an ovoid cross-sectional outline becomes more spherical with a rise in internal tension. It has been ascertained with small to moderate resting intrauterine tensions that the displacement is large when compared to the acting tension and varies in a manner proportionate to the tension. With high resting internal tension, the displacement resulting from an increase of tension is small in comparison to the acting tension and not proportionately related to tension changes. With extremely high resting intrauterine tension, such as occurs in abruptio placentae, the displacements are very small.

2. The displacement component present and associated with uterine contractions in which there is either a localized or generalized thickening of the uterine wall.

3. The displacement produced by the resultant of acting forces tending to pull the organ anteriorly.

From our study it was apparent that displacements associated with uterine activity may be symmetric or asymmetric, localized or generalized, rhythmic, or arrhythmic, of the same intensity or of variable intensity, and at the same time, the tone level as reflected in the abscissae may remain constant or fluctuate above and below the arbitrary selected base line. The recordings obtained with the recorders used show changes in rhythm, intensity, and tone level. On the other hand asymmetric, symmetric, localized, or generalized uterine activities are indicated by notations placed on the recordings at the time of their observance.

We have found it necessary to distinguish between large and small contractions. The large are conventionally known as the Braxton Hicks of prelabor and are usually characterized by the generalized and coordinated nature in which the uterine muscle contracts. They are of relative long duration, and of relative great magnitude. These contractions have attributes similar to the prodromal or early intermittent contractions of labor and ultimately manifest themselves as true labor con-

tractions associated with the intermittent pains of labor. There is evidence of bilateral sources of excitation in which symmetrical halves of the uterus may be under the influence of separate excitation centers, this accounting for some asymmetric responses. Notations made on the recordings indicate that each half of the uterus responded asynchronously.

Theoretically, normal excitation and symmetrical action may involve either synchronous excitation from two sides, or asynchronous excitation in which the excitation developing from one side precedes that of the other side, or the excitation may involve but one side only.

The small contractions are of particular interest and are found present during pregnancy and labor. These contractions are characterized when present by their rhythm, relatively low amplitude and short duration. Singly or in combination with the large contractions they are apparently concerned in producing the changes known to take place in the lower uterine segment, previous to and during labor. Hence, they may be considered as evidence of preparatory uterine activity.

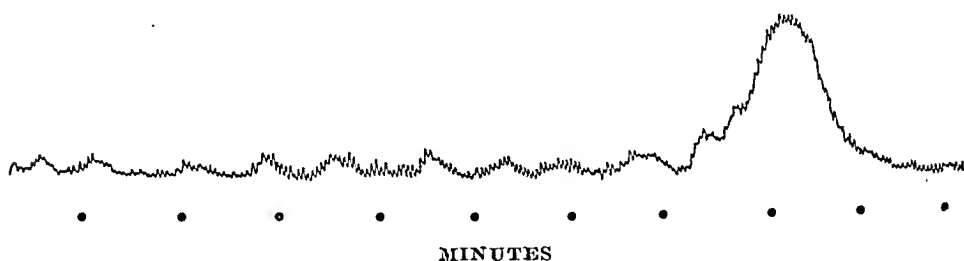


Fig. 5.

This activity may thus account for the placental separation in marginal or central placenta previa with the associated painless bleeding. Furthermore, the small contractions may be of such intensity during prodromal labor to call subjective attention to their presence as back pain, usually continuous but associated with exacerbations, having a frequency comparable to the frequency of the small contractions.

It is believed that the small contractions are derived from localized activity of the fundal musculature. Rhythmical excitation of limited range may account for their presence. There is evidence that such excitation may spread in a progressive manner to adjacent muscle until the whole of the uterine muscle is involved in a generalized coordinated response (Fig. 5). Caution must be exercised in identifying the small contractions. It is necessary to exclude the periodic fetal rolling movements and periodic variations in the amplitude of maternal respiration, particularly the variations occurring in the inspiratory phase of respiration.

That the large and small contractions may differ fundamentally one from the other may be surmised in view of the responses obtained with

oxytocic agents. The initial response in some instances is related to the excitation of those factors operating to produce the small contractions.

With reference to the statistical analysis, the evident tendency for larger uterine displacements in multiparas is primarily due to the general larger uterine size. The apparent difference in the over-all duration of the contractions in the two classes is due in part to a difference in the duration of the contraction and relaxation phases. There may exist fundamental differences in the manner of excitation, conduction, and response of the uterine muscle of the multiparas as compared to the primiparas. On the other hand, it is believed that selection of normal primiparas and normal multiparas, gravida ii to iv, of the same uterine size, same relative states of labor will show no significant differences in the temporal relationships of the individual contractions or phases.

The improvements in the findings which occurred with the elimination of pathologic and abnormal cases and the utilization of findings limited to those conforming to the standards set up is of interest. Apparently the excluded cases were the source of motility components, serving to modify the findings of the "normal." There exists a possibility that the excluded cases may be characterized by their specific abnormal motility.

The persistence of large standard deviations for the "normals" is in part indicative of the prevalence of compound and complex contractions. These contractions are evidences of incomplete or abnormal coordination of uterine muscle activity. They are present in patients having normal labor activity and are especially prevalent in early labor.

The increased durations of the contractions following rupture of the membranes is explained by a significant increase in the contraction phase. This is in line with the general clinical facts that with the loss of fluid, the intensity of the pains increase and the duration of the pains increase. The factor of ruptured members, apparently operates to modify the character and course of uterine motility during labor. Furthermore, we are of the opinion that spontaneous premature rupture of the membranes is not the cause of labor but the result of prodromal labor activity. This statement is qualified to the extent that it applies only to those patients at term and who have not been subjected to physical violence. Furthermore, in these patients the duration of clinical labor is the same, or less on the average than the duration of labor in patients with intact membranes.

There is a great deal of difference in respect to the time of admission and onset of clinical labor. Patients are urged to come to the hospital immediately upon notice of loss of fluid or blood per vaginam, irrespective of the presence or absence of pains. In these patients the time of admittance cannot be regarded as the onset of clinical labor, nor can the time of rupture of the membranes be considered as the onset of clin-

ical labor. Recordings were made on several patients resting in bed in whom the membranes ruptured spontaneously. The contractions recorded were not associated with pain and in fact the contractions were of insufficient strength to cause rupture of normal membranes.

The treatment of patients with spontaneous premature rupture of membranes should be correlated with motility studies. In view of the findings, it is not advisable as a routine procedure to stimulate with oxytocics the uteri of term patients with ruptured membranes, since danger of over activity may result in rupture of the uterus. The use of mild oxytocics is indicated when there is no progressive improvement of motility of recognizable quality twenty-four hours after the supposed rupture of the membranes. The absence of progressive improvement of motility suggests either unruptured membranes or an abnormal motility state.

The specific findings obtained by statistical analysis serve to provide standards for comparisons. The findings from any single or series of cases may be compared with those obtained from a large series of cases. One application is illustrated in the following manner: The uterus of a term multipara was stimulated with galvanic current using bipolar leads. As a result of this procedure, there was a pronounced change in the type of motility which persisted for thirty minutes. During this period there occurred four contractions having the following means: Contraction phase, 360 seconds; relaxation phase, 51 seconds; over-all duration, 411 seconds. Applying methods of statistical analysis, it is possible to predict that 99.7 times out of a hundred the observation in respect to the contraction phase and over-all duration were significant and not due to chance.

SUMMARY

1. A standardized method for making temporal analysis of uterine displacement curves is presented.

2. Additional evidence in respect to two fundamentally important uterine displacement components, namely, the large and the small, is presented.

3. Accumulated findings have been subjected to statistical analysis in which the displacement in centimeters, the duration in seconds of contraction phase and relaxation phase, and over-all duration were investigated in unselected and selected cases. Arithmetical means and standard deviations were determined and significance ratios ascertained by use of the standard error.

4. The application of the findings for assay purposes is illustrated in the text.

CONCLUSIONS

1. The displacements tend to be larger in the unselected multiparas than in the unselected primiparas, due in part to the difference in the size of the uterus.

2. The unselected multiparas as a class have longer contractions than the unselected primiparas as a class, due to combined increase in contraction and relaxation phases.

3. The data from selected cases have frequency distribution curves, showing less skewness and more symmetry than unselected cases. Selected cases provide means and standard deviations which represent the normal according to the standards established for analysis. Unusual and pathologic cases may possess specific abnormal motility. Selected multiparas and selected primiparas, standardized with one another, will show no significant difference in the temporal relationships of the large contractions.

4. Under standard conditions a spontaneous plus or minus 27 per cent change in the frequency of large contractions represents the average expectations.

5. Anterior displacement of the abdominal wall during an uterine contraction can be explained by purely physical means, change in cross-sectional outline, thickening of the uterine wall, and action of forces pulling the uterus forward.

6. Large and small contractions, independent or dependent upon one another, serve a useful function in preparing the lower uterine segment for labor.

7. Labor motility is inaugurated in advance of the development of labor pains.

I wish to express my gratitude to Drs. F. L. Adair and M. E. Davis for their helpful cooperation, timely advice, and suggestions during the course of this study.

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The author reports a remarkably high incidence of syphilis in an unselected group of 500 women and 1,000 men in his clinics (Rio de Janeiro). It is noted, however, that most of the patients are in a roughly selected class as they all have cardiovascular complaints. Of 500 women, 137 (31.4 per cent) were found to be syphilitic by clinical, serologic and in some instances post-mortem findings. Of 1,000 men, 470 (47 per cent) were syphilitic.

A group of 349 cases was divided as follows: secondary syphilis 17, tertiary syphilis 185, central nervous system syphilis 9, latent syphilis 111, and heredosyphilis 27.

The author concludes that the popularization and employment of individual methods of protection should be the basis of the attack on the problem of syphilis.

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WOUND DISRUPTION AND ITS MANAGEMENT*

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THE high mortality which attends the disruption of abdominal wounds makes this postoperative complication vitally important. Fortunately, it is of relatively infrequent incidence but, nevertheless, may at times contribute quite noticeably to the list of preventable fatalities. Any procedure, which may be of material value in reducing postoperative mortality, is deserving of serious consideration. It is for this reason that our study of wound disruption and its management is presented.

From 1933 to 1940, there were never over one or two eviscerations on our service of 1,300 laparotomies a year, so that very little attention was directed to this infrequent complication. However, when six occurred in 1940 with a mortality of 50 per cent, an investigation and analytic study were made. Considerable interest was aroused when it was found that the three deaths were in patients who were in good condition at the time of evisceration, were repaired layer by layer, and died of peritonitis. The two patients repaired by simple through-and-through suture of all layers lived. Believing this relationship of type of repair to mortality to be more than coincidental, we decided to study all the cases of wound disruption occurring on the gynecological service from January, 1933, to July, 1941, a period of eight and one-half years. Records beyond this period would not permit a careful study and accurate analysis of the individual cases. We were particularly interested in finding the most common causes of wound disruption. But above all, we wanted to determine how important the type of secondary closure was in affecting the mortality rate.

Brettauer,¹ in 1899, was the first to describe this condition in the American literature with a report of three cases. Larger series have since then been reported by Madclung,² Sokolov,³ Melency and Howes,⁴ Glenn and Moore,⁵ and Fallis.⁶ The collective review of 1,458 cases of disruption by Hartzell and Winfield,⁷ in 1939, gives an excellent summary of the literature. One is impressed with the variety of statistics and opinions as to etiology and management of this complication. This, in itself, indicates that the contributing factors are many and the management is not a universally accepted routine.

*Read at the regular meeting of The Chicago Gynecological Society on November 21, 1941.

Absolute prevention of this complication is impossible, as mentioned by Downs.⁸ For, notwithstanding the many articles written in the past decade regarding the importance of suture materials and the methods of applying them, there still remains a definite incidence of wound disruption. Therefore, a concerted effort should be made to minimize the incidence and cautiously manage those cases which must inevitably occur. That the incidence can be lowered is clearly demonstrated by Glenn and Moore⁵ who discovered important etiologic factors in their first study which they believe have improved the results in the second report.

A review of the 10,725 laparotomies done on the gynecologic service during the past eight and one-half years revealed 16 eviscerations or total abdominal wound disruptions (Table I). The incidence of 0.15 per cent is comparatively low (average reported 1.83 per cent). Noteworthy are the 11 deaths in these 16 cases, revealing a high mortality of 68.7 per cent (average reported 34.8 per cent). The day of disruption varied from the second postoperative to the twelfth, average being the seventh (Table II).

TABLE I. INCIDENCE OF DISRUPTIONS

Total number of laparotomies (Exclusive of McBurney's incisions)	10,725
Number of total disruptions	16
Incidence of disruption	15 per cent
Number of deaths following disruption	11
Mortality in disruptions	68.7 per cent

TABLE II. CONTRIBUTING FACTORS

FACTOR	FREQUENCY
Severe coughing	9 cases
Severe emesis	9 cases
Abdominal distention	8 cases
No tension sutures	6 cases
Infected wound	8 cases
Drain through wound	2 cases
Obese wall	2 cases
Malignancy	0 cases

The most common factors associated with these 16 cases of disruption were: cough, 9 cases; emesis, 9 cases; distention, 8 cases; no tension sutures, 6 cases; infected wounds, 8 cases; drain, 2 cases; obese wall, 2 cases; and malignancy, 0 cases (Table II).

The type of secondary closure in these 16 cases was as follows: 7 closed layer-by-layer, 7 by simple through-and-through suture including all layers, 1 by tampon and adhesive bridges, and 1 patient died before any treatment could be instituted. Of the 7 cases closed layer-by-layer, 6 patients died, all of peritonitis. Of the 7 closed by simple through-and-through suture only 3 died, 1 due to peritonitis (pelvic abscess was present at time of repair), 1 due to bronchopneumonia, and 1 due to a pulmonary embolus. The only patient treated with tampon and bridges died on the day of evisceration due to cardiac failure (Table III).

TABLE III. DAY OF DISRUPTIONS

CASE AGE	DIAGNOSIS	OPERATION	PRIMARY CLOSURE*	DAY DISRUPTION†
1. M. B. 33	Fibroid uterus Ventral hernia	Supracervical hysterectomy Repair of hernia	cgg no tensions	PO IX
2. C. S. 49	Fibroid Chronic salpingitis	Supracervical hysterectomy Salpingo-oophorectomy	cgg swg tensions	PO VI
3. E. N. 39	Chronic pelvic inflammatory disease and cysto-urethrocele	Laparotomy Vaginal plastic	cgg swg tensions	PO VI
4. A. K. 50	Fibroid Diabetes	Supracervical hysterectomy Salpingo-oophorectomy	cgg no tensions	PO VII
5. L. K. 26	Pseudomucinous cyst of ovary	Supracervical hysterectomy Salpingo-oophorectomy	cgg swg tensions	PO V
6. E. B. 38	Fibroid	Supracervical hysterectomy Salpingo-oophorectomy	cgg swg tensions	PO VII
7. D. J. 45	Fibroid Chronic salpingitis	Supracervical hysterectomy Salpingo-oophorectomy	cgg swg tensions	PO IX
8. M. M. 38	Fibroid Chronic cervicitis	Total hysterectomy	cgg swg tensions	PO V
9. L. M. 53	Degenerated fibroid Cardiac	Total hysterectomy	cgg no tensions	PO XII
10. D. B. 41	Left ovarian cyst Adhesions	Left salpingo-oophorectomy	cgg no tensions	PO III
11. A. K. 56	Fibroid Chronic pelvic inflammatory disease	Supracervical hysterectomy	cgg swg tensions	PO IX
12. M. G. 34	Fibroid Chronic salpingitis	Supracervical hysterectomy	cgg swg tensions	PO II
13. M. J. 45	Fibroid Chronic salpingitis	Supracervical hysterectomy	cgg swg tensions	PO VIII
14. H. W. 38	Fibroid Chronic salpingitis	Supracervical hysterectomy Salpingo-oophorectomy	cgg no tensions	PO VII
15. M. R. 65	Fibroid Prolapse	Myomectomy and suspension Colporrhaphy	cgg drain no tensions	PO VII
16. M. J.	Fibroid Chronic salpingitis	Total hysterectomy Salpingo-oophorectomy	cgg drain no tensions	PO XII

*cgg, chromic catgut; swg, silkworm gut.

†Po, postoperative.

It is interesting to note that Bettman and Lichtenstein⁹ in their review of 7,500 laparotomies at Michael Reese did not think that coughing, emesis, infection, and omission of tension sutures were of great etiologic importance. However, the summary by Hartzell and Winfield⁷ indicated that conditions which increase the intra-abdominal pressure are contributing factors in wound disruption. Reading through these charts, especially noting the interns' and nurses' progress notes, in a majority of these cases the evisceration seemed imminent a day or so before it occurred.

Only two of the patients had drains (12½ per cent), but this is a relatively high percentage since very few laparotomies are drained through

TABLE IV. CAUSE OF DEATH

CASE	CONDITION AT TIME OF DIS- RUPTION	SECONDARY CLOSURE	ANESTHETIC	RESULT*	CAUSE OF DEATH
1. M. B.	Fair	Layers	Ether	Died PE III	Peritonitis
2. C. S.	Poor	Layers	Ether	Died PE I	Peritonitis
3. E. N.	Terminal	No repair	0	Died immediately	Peritonitis and bron- cho pneu- monia
4. A. K.	Fair	Through-and- through braided silk	Ether	Died PE I	Broncho- pneumonia
5. L. K.	Good	Through-and- through braided silk	Ether	Home PE XX	----
6. E. B.	Poor (abscess)	Through-and- through braided silk	Nitrous o x- ide	Died PE VIII	Peritonitis
7. D. J.	Good	Through-and- through braided silk	Ether	Died PE III	Pulmonary embolus
8. M. M.	Good	Layers	Nitrous o x- ide	Died PE XVII	Peritonitis
9. L. M.	Poor cardiac	T a m p o n a n d bridge	0	Died PEO	Cardiac fail- ure
10 D. B.	Poor	Layers	Ether	Home PE XI	----
11. A. K.	Good	Layers	Cyclo pro- pane	Died PE V	Peritonitis
12. M.G.	Good	Layers	Spinal	Died PE III	Peritonitis
13. M. J.	Good	Through-and- through silk- worm gut	Cyclo pro- pane	Home PE XVII	----
14. H. W.	Poor	Through-and- through silver wire	Spinal	Home PE 60	----
15. M. R.	Good	Layers	I. V. Pentothal	Died PE VI	Peritonitis
16. M. J.	Poor	Through-and- through braided silk	I. V. Pentothal	Home PE XVIII	----

*PE, Postvisceration.

the wound on our service. When we consider the logical explanation of wound dehiscence by Freeman¹⁰ as being due to an omental wedge forcing its way through an incompletely closed peritoneum, obviously a drain invites such a process, the actual rupture being precipitated by sudden coughing, sneezing, or emesis.

Most authors have reported a definite incidence of malignancy among these cases (average 22 per cent) which suggests this condition as a likely contributing factor. However, we found no cases of malignancy in this group of complete disruptions. This seems more unusual when one considers the large number of laparotomies for malignant cases on our service. Many patients with Group III and IV carcinoma of the cervix

have had laparotomies for internal iliac artery ligation and for pelvic sympathectomy. These patients would seem very poor risks, owing to the far-advanced carcinoma and previous extensive radiation. Yet only one patient had a *partial* evisection on the tenth day (Greenhill and Schmitz¹¹).

Much has been written about the importance of vitamin C in wound healing. Wolfer¹² demonstrated low ascorbic acid levels in patients at the time of evisection. On our service on this basis, one would expect many wounds not to heal. It must be remembered that our patients are nearly all poor negroes and whites, most often in a state of avitaminosis. Also, we do not give ascorbic acid to these patients routinely either pre- or postoperatively. Just the occasional case with a noticeable avitaminosis receives vitamin therapy. The same can be said of hypoproteinemia; even though it has been shown to be a contributing factor by the work of Thompson, Ravdin, and Frank.¹³

The type of suture material has been stressed as an important factor.

Whipple and Elliott¹⁴ advise the use of silk in abdominal closure. Spool cotton throughout is advocated by Meade and Ochsner.¹⁵ Closure of the abdomen by through-and-through silver wire sutures in all cases, where there is likely to be infection or excessive strain, has been used successfully by Reid, Zininger, and Merrell.¹⁶ Babcock¹⁷ reports the allergic reaction of tissues to chromic catgut as a cause of wound disruption. Norris¹⁸ points out the loss of tensile strength with iodized catgut, due to an increased perishability rate because of the destructive action of iodine on the catgut.

However, our methods have been rather contradictory to the above teachings. Because we have eight different services in our department of gynecology, eight different methods are used to close the abdomen. All of the surgeons use iodized catgut, but in addition some use fine silk, heavy silk, silver wire, and silkworm gut. All abdomens are closed in layers, i.e., peritoneum, transversalis fascia, rectus fascia, subcutaneous layer (if thick), and skin. About two-thirds of the operators use tension sutures and one-third do not. Also interesting is the fact that most of these abdomens have been closed by interns, after a few demonstrations.

A consideration of all these seemingly contradictory reports brings up the question as to what is the cause of wound disruption. Obviously, disruption is due to a disturbance in wound healing.

According to Mason¹⁹ the process of healing may be divided into three phases, i.e., (1) *Exudative* or lag period, lasting four to five days during which the strength of tissue union is low. (2) *Fibroblastic* stage, from the fifth to the sixteenth day when the wound attains the maximum strength afforded by a connective tissue scar. (3) *Stage of maturation* or differentiation for fascia, tendon, and bone.

Keeping this fundamental process in mind, it is logical to believe that any one of many factors may be responsible for the disruption. These factors may be classified for convenience as follows:

A. *General Conditions:*

1. Type of patient, obese, asthenic
2. Malnutrition, hypoproteinemia
3. Avitaminosis, low ascorbic acid level
4. Dehydration
5. Malignancy, especially if previous radiation has been given
6. Presence of acute or chronic pelvic inflammation

B. *Local Conditions:*

1. Method of primary closure, failure to make careful anatomic layer-by-layer closure
2. Type of suture, strength and lasting ability insufficient
3. Size and quantity of suture, too heavy and too much
4. Interference with blood supply of tissues, too tightly sutured
5. Irritants such as strong antiseptics and *drains*
6. Presence of hemorrhage and blood clots in wound
7. Infection in wound
8. Failure to provide rest and immobilization of wound until fibroplasia is well established (twelve to fourteen days)

C. *Unexpected Postoperative Complications:*

1. Abdominal distention
2. Severe coughing
3. Persistent emesis
4. Hiccoughing
5. Sitting up or getting up too soon.

Such a list of indirect causes would explain why the number of good reports of the past decade seem contradictory. A consideration of this list also explains why there will always be eviscerations and why a good method of management is essential.

An evisceration is a true surgical emergency and gives one the same sort of uneasy feeling as to observe an eclamptic convulsion.

A good description of this complication by Shipley²⁰ is as follows: "The edges of the wound are usually necrotic, the different layers are more or less sealed together with the exposed intestine dull in color and often covered by exudate—one hates to be called to see them."

It is the type of complication which makes the surgeon feel embarrassed, as though his technique were faulty. But in our series, all the operators in the department had this complication, and there was no preponderance of incidence on any one service. The treatment must be carefully decided according to the best interests of the individual case.

When evisceration occurs, the first consideration is whether the patient's condition is satisfactory to withstand a secondary closure. If there is already a generalized peritonitis, pelvic abscess, severe cardiac

pathology, or pneumonia, this patient is best treated with sterile gauze tampon and firm adhesive strapping. Several days later, when the patient is improved, a satisfactory secondary closure may be done.

If secondary closure is to be done at the time of evisceration, the patient is given $\frac{1}{4}$ gr. of morphine, strapped with adhesive, advised against coughing or straining, and taken to the operating room. The type of anesthesia is very important, especially since many of these patients have been coughing for several days before this accident. General anesthesia is to be avoided if at all possible. One of the patients in our series died of a bronchopneumonia which was attributed to the ether anesthesia for secondary repair. Now intravenous or spinal anesthesia is preferred. Local infiltration has been used, but infiltration of an infected area is unsatisfactory and dangerous.

The surgical preparation is quite simple. Since the tissues exposed are all potentially infected, we just clean the surrounding skin with normal saline and alcohol, avoiding any excessive manipulation of the exposed bowel. We do not believe strong antiseptics or meticulous cleansing procedures are indicated or worth while in this instance.

A nonabsorbable type of suture is used which may be a No. 12 braided silk, silver wire, or silkworm gut. No attempt is made to separate and identify the layers of the abdominal wall, as this would mean considerable manipulation of an infected area. Besides, this is unnecessary for good closure and adds to the possibility of peritonitis which is the most common cause of death following evisceration. With a large cutting-needle on each end, the suture is brought through the entire wall from within the peritoneal cavity to the skin surface, two inches from the edges. These sutures are not tied but held taut until all have been placed ($1\frac{1}{2}$ inches apart). This makes the insertion of the last few easier; also the tying is an important procedure for good apposition. As the operator draws these through-and-through sutures up for tying, the assistant keeps his hand inside the peritoneal cavity for two reasons; first, to make sure that the peritoneum is closely approximated, and second, to prevent a loop of bowel from being caught in the closure.

Now the postoperative care becomes more important than ever: adequate fluids to combat dehydration, 3,000 to 4,000 c.c. a day, a high protein diet, and 300 mg. of ascorbic acid daily. All coughing must be prevented by sufficient sedation; a Wangensteen suction for upper abdominal distention or vomiting and a Miller-Abbott tube for small bowel obstruction. Chemotherapy in the form of 100 c.c. of 5 per cent sodium sulfathiazole may be given intravenously as needed for peritonitis. The sutures are left in place until healing is complete; this may take three weeks. The patient is then allowed up. These patients must be examined carefully in six weeks for a ventral hernia.

One may ask why we feel so certain that simple through-and-through secondary closure is the best method. There are two good reasons to

substantiate this thought. First, it is an accepted surgical principle that the least amount of trauma and manipulation in an infected field is to be preferred. To do a layer-by-layer repair one must dissect these layers apart, then puncture each layer many times with a needle and introduce a relatively large amount of suture to retard healing. Second, and most important, our analysis of the 16 cases in the past eight and one-half years bears this out. Of the seven cases closed in layers, 6 of the patients died of peritonitis and 4 of these were in good condition at the time evisceration occurred. Of the 7 cases closed by simple through-and-through suture, 3 patients died, but only one because of peritonitis; this patient had a pelvic abscess at the time of evisceration. The other two deaths were due to pulmonary embolus and bronchopneumonia following a general anesthetic.

A careful study of the wound disruptions on another surgical ward during this same period of eight and one-half years was made. In 1,366 laparotomies, there were 6 eviscerations, an incidence of 0.44 per cent (ours 0.15 per cent) which corresponds with Hesselstine's²¹ report from the Chicago Lying-in Hospital. There was one death, a mortality rate of 16.6 per cent (ours 68.7 per cent). However, a more interesting fact is that only one case was repaired in layers and this was the patient that died of peritonitis. The 5 patients that recovered had a simple through-and-through closure. One of these cases which eviscerated twice is of interest. The patient was treated conservatively by tampon and bridging until her condition improved, when a satisfactory closure could be made. She recovered.

A careful analysis of the case histories in this group of wound disruptions has been interesting and very educational for us. One becomes evisceration-conscious in his work after such a study. It has often been said that good postoperative care means the treatment of complications before they arise. The incidence of wound disruption can be lowered by keeping in mind the contributing factors as mentioned before. The high mortality of this complication can be reduced by this simple through-and-through type of secondary closure.

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DISCUSSION

DR. H. CLOSE HESSELTINE.—This paper covers the various conditions which have been charged with contributing to disruption of abdominal wounds. The method and management of the secondary closure are in accord with most of the recent reports, namely, closure with the least possible manipulation with non-absorbable suture material, usually by mass suturing rather than individual tissue approximation, the appropriate treatment for complications, such as peritonitis and cough.

The incidence reported by Dr. Schmitz and Dr. Beaton is very much below that which has been given as the average. On the other hand, the mortality in their group is appreciably higher than the average. Perhaps the mortality rate does not result so much from the disruption as it does from the condition which may have been more or less responsible for the disruption, such as peritonitis.

Bohlender and I made a report in 1940 before this Society of our observations of this complication at the Chicago Lying-in Hospital. At that time, we reported 15 eviscerations in 3,179 abdominal operations, an incidence of 0.47 per cent. Since the compilation of those data, there have been 935 abdominal operations, both obstetric and gynecologic, without a single abdominal disruption. This apparent improvement seems to have resulted from exercise of greater care in the primary closure and by combating those conditions which may predispose to evisceration. Ordinarily, most of our patients are in good health and on a fairly well-balanced diet. Although sufficient determinations have not been made, it has been assumed that our patients are usually not deficient in vitamin C. We have made no attempt to administer ascorbic acid or to prescribe high protein diet pre- or postoperatively.

It does not seem justifiable to follow a routine for every patient, in accordance with recent suggestions, of a three- to four-day preparation with a high caloric diet, high protein, and high vitamin C and B. This should apply only to those actually in need of one or more of the factors.

DR. CHARLES E. GALLOWAY.—Probably the reason why such a large number of eviscerations is reported is that the interns in the County Hospital close the wounds. I am glad to hear this problem stressed, because otherwise there will be 15,000 eviscerations in the United States every year and about four or five thousand of the patients will die.

DR. SCHMITZ (closing).—Concerning closure of the wounds by interns, I would like to say that in this series the attending surgeons closed the peritoneum, and they, therefore, are probably responsible for the end results.

A STUDY OF CONTRACTIONS IN LABOR BASED ON
KYMOGRAPHIC RECORDS OBTAINED FROM
AN INTRAUTERINE BALLOON

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MOST obstetricians will agree that the efficiency of uterine contractions is the single most important factor in the mechanism of labor. Failure of the uterus to contract normally and to relax adequately between contractions results in slow dilatation of the cervix, incomplete flexion of the fetal head, delay in normal rotation, and slow descent. Much emphasis has been placed in the past upon the maternal pelvis and its relation to cephalopelvic dystocia. Adequate diagnostic means are now available for the measurement and classification of the pelvic diameters, thus permitting the obstetrician to predict with fair accuracy any impending dystocia between the fetal head and the birth canal. Unfortunately, no precision instrument such as the x-ray is available for the study of uterine muscle physiology.

Factors influencing the contractions of uterine muscle fibers have received much attention in recent years, but still we do not know why the uterus contracts. That smooth muscle has the capacity for intrinsic motility is well known. There must be several factors, physical and chemical, which determine the nature of the contractions. A recent report on uterine motility¹ makes it clear that the hormones play an important part in the initiation of contractions and their pattern after they have been established. It has now been shown that both estrogen and progesterone fall off sharply a few days before the onset of labor. In the pregnant uterus at term, the hormones must play an important role, the nature of which is not understood. More important perhaps than the chemical factors may be those of a purely mechanical nature. It has been suggested that the onset of labor may result from distention, which puts the muscle fibers under tension; ischemia results and contractions follow.² The well-known fact that artificial rupture of the membranes at term will induce labor tends to invalidate the distention theory as the cause of labor.

The nature of these contractions has been studied by several investigators. The first of these to use an intrauterine balloon for recording contractions on a kymograph was Sehatz³ in 1872. Rucker,⁴ in 1925, used the Voorhees bag and recorded the tracings of uterine contractions in labor. He demonstrated graphically for the first time the oxytocic ef-

fect of posterior pituitary extract. Many reports have appeared since that time, most of them concerned with studies on excised musele. Others have utilized a distended balloon in the cervix. As far as I know, this is the first report on uterine contractions studied by means of a distended balloon in the active, contractile portion of the fundus uteri with the membranes intact. This report will describe the normal uterine contractions of spontaneous labor at term and the effect of ruptured membranes on the pattern of uterine motility.

TECHNICAL PROCEDURE*

The observations recorded here were made upon young primiparas who were under my care at the Evangeline Booth Hospital in Richmond. Their cooperation was obtained without difficulty. In the 22 cases studied to date by the technique to be described, there has been no instance of intra-partum or post-partum complication resulting from the experimental procedure. In order to study the effect of ruptured membranes upon uterine contractions, it was necessary to select patients in whom the balloon could be passed extraovularly without injury to the membranes. By recording the contractions in such a case with intact membranes and then observing the change which occurred when the membranes rupture, a basis of comparison was established. Four cases who fulfilled these requirements have been selected from the total group and the tracings upon these comprise this report.

A small condom balloon was attached to a specially designed linen catheter, somewhat heavier than that used by the urologist for ureteral catheterization. The catheter was long enough to permit insertion of the balloon well up into the fundus and still permit its opposite end to protrude from the vagina. It was necessary to pass the balloon early in labor before the presenting part became fixed in the pelvis. With the aid of a uterine dressing forceps, it was possible to insert the balloon between the membranes and the uterine wall, leaving the amniotic sac undisturbed. The catheter was then connected by a rubber tube to the mechanical ink recorder. The system was filled with sterile water, the rubber tube and catheter having been previously sterilized, and sufficient water was introduced to raise the pressure to 80 mm. of mercury. The tracings of uterine contractions were then recorded on a revolving kymograph equipped with a timer. The catheter and balloon were allowed to remain in the uterus throughout labor and were expelled after delivery of the fetus.

CASE 1.—The first patient was permitted to go through labor without interference and the membranes ruptured spontaneously during the early part of the second stage. The first stage of labor was considered to end after full dilatation of the cervix, regardless of the state of the membranes. The first tracing was taken two hours after the onset of labor. Contractions occurred every five to seven minutes, were relatively low and somewhat variable in amplitude, and there was a moderate degree of tetany. This is the typical picture of early first-stage contractions (Fig. 1). As labor progresses to full dilatation of the

*The illustration of the instrument for this procedure was published in this JOURNAL 42: 1024, 1941.

cervix, there is a marked change in the pattern of uterine contractions. The second tracing on this case taken early in the second stage, thirty minutes after full dilatation, shows considerable increase in the degree of tetany. The contractions occur at more frequent intervals, every

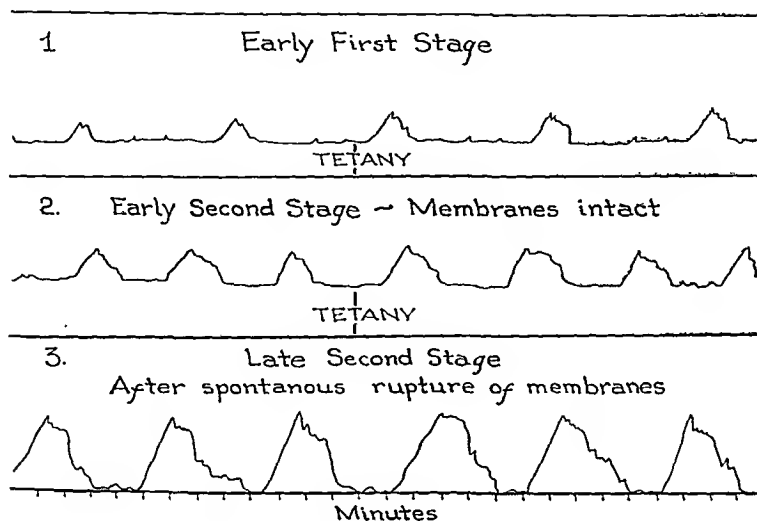


Fig. 1.—Case 1. After spontaneous rupture of the membranes, the uterus loses its tetany, relaxes between contractions, and each contraction becomes more efficient. Note in this and all other tracings that the duration of contractions may sometimes be as long as three minutes. Uterine contractions begin some time before they can be palpated or perceived by the patient. Actually the patient experiences pain during a relatively short interval in any contraction.

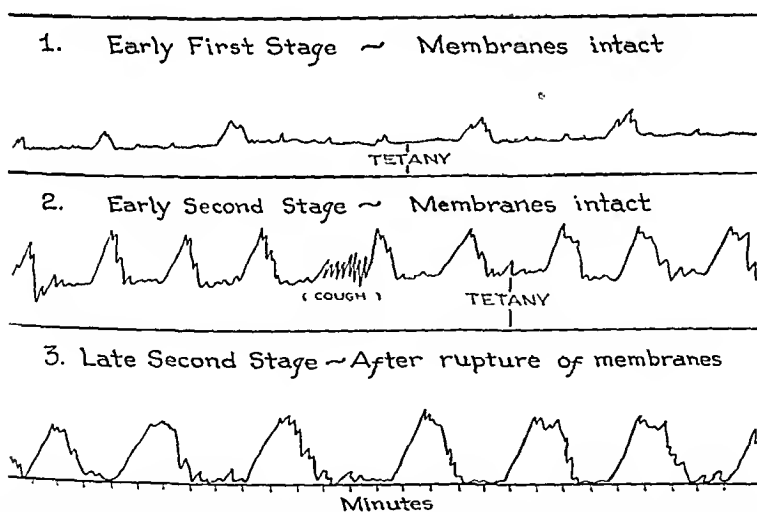


Fig. 2.—Case 2. After spontaneous rupture of the membranes in the second stage, the uterus loses its tetany, relaxes between contractions and the amplitude of each contraction increases.

three minutes, have a somewhat longer duration, but the actual excursion of each contraction is not increased because the tetany prevents full relaxation between contractions. The membranes ruptured spontaneously thirty minutes after the second tracing was taken. It will be observed now that tetany has been abolished; and as a result, the ampli-

tude of each contraction is increased. The relaxation of the uterus following spontaneous rupture of the membranes during the second stage greatly increases the efficiency of each contraction (Fig. 1).

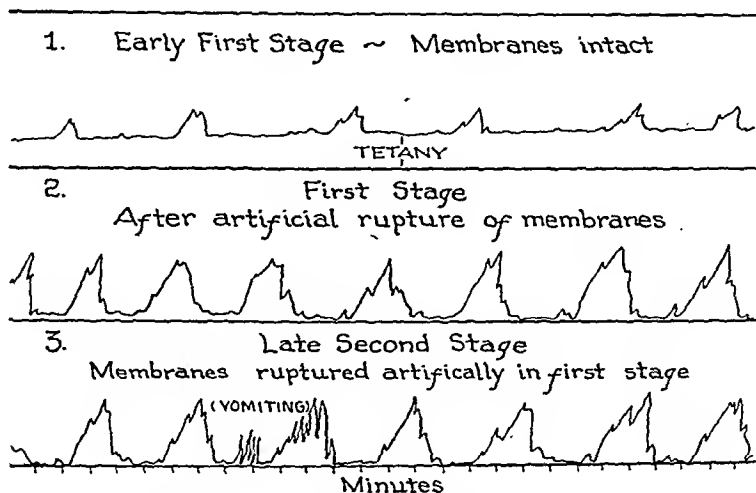


Fig. 3.—Case 3. After artificial rupture of the membranes during the first stage, tetany is abolished and the contractions assume the high amplitude seen after spontaneous rupture.

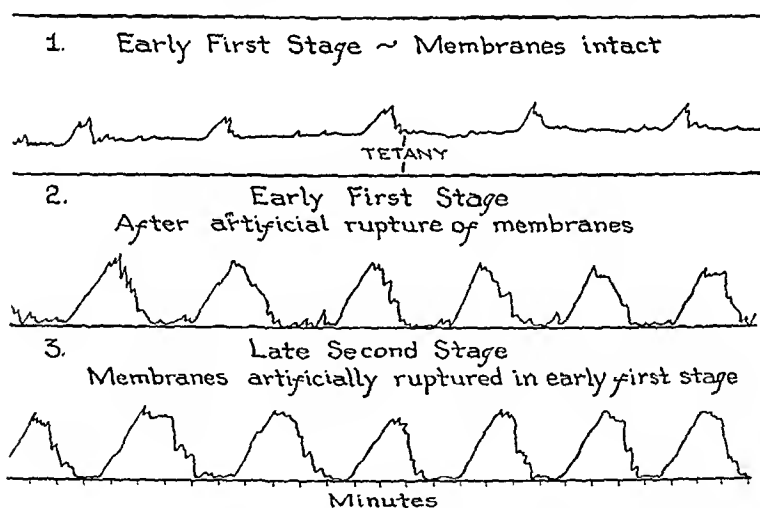


Fig. 4.—Case 4. After artificial rupture of the membranes during the first stage, the uterus loses its tetany and the contractions increase in amplitude such as occurs after spontaneous rupture during the second stage.

CASE 2.—The first tracing was taken on this patient three hours after the onset of labor. These early first-stage contractions show a relatively low, somewhat variable amplitude superimposed on a moderate degree of tetany. During the early second stage and while the membranes were still intact, it may be seen that the tetany has increased. The contractions became more painful, but in spite of this their expulsive efficiency was not augmented because of the tetany. One hour and twenty minutes after this tracing the membranes ruptured spontaneously. The tracing taken during the late second-stage showed the absence of tetany

with a much higher rise in each excursion of the writing point. It must follow that the efficiency of each contraction is thereby increased (Fig. 2).

CASE 3.—Early first-stage contractions recorded two hours after the onset of labor showed the irregular, low amplitude, mildly tetanic contractions characteristic of this stage of labor. In this case the membranes were ruptured artificially immediately after the first tracing was recorded. The second tracing taken one hour later and before the cervix was fully dilated reveals the absence of tetany. Even before the end of the first stage, the uterus relaxed between each contraction. The tracings assumed the high amplitude characteristic of second-stage contractions after spontaneous rupture of the membranes. The third tracing taken during the late second stage shows that the pattern of motility which follows rupture of the membranes persists throughout labor (Fig. 3).

CASE 4.—The early first-stage contractions are similar to those already described. Immediately after this tracing was taken the membranes were ruptured artificially. The second tracing taken thirty minutes later shows that tetany has been abolished and each contraction assumes the high amplitude characteristic of the uterus which relaxes adequately between pains. The third tracing taken during the late second stage shows that the pattern of motility produced by artificial rupture of the membranes persists throughout labor (Fig. 4).

CONCLUSIONS

1. The extraovular, high fundal, intrauterine balloon connected to a mechanical ink recorder has been used to study the patterns of uterine motility during labor.

2. Labor contractions during the early first stage have a relatively low amplitude superimposed on moderate tetany. As labor progresses with intact membranes tetany becomes more marked.

3. Labor contractions after rupture of the membranes, spontaneous or artificial, are characterized by the absence of tetany. The increased amplitude which results augments the expulsive efficiency of each contraction.

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AN ANALYSIS OF ABORTION DEATHS IN THE DISTRICT OF COLUMBIA FOR THE YEARS 1938, 1939, 1940

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IN THE cities where maternal mortality studies have been made, a noticeable reduction in the number of deaths has been reported. Physicians who have attended the meetings of such committees or have been members of the committees are all aware of the sobering effect of the verdict "death preventable—responsibility assigned to the physician because of lack of judgment." Accordingly, by these means the profession has succeeded in raising its own standards of maternal care to a considerable degree but has devised no effective control over the abortionist as yet.

The committee on maternal mortality of the District of Columbia has been functioning since June, 1937. It reports that 24 per cent of maternal deaths in the District are due to abortions.^{4, 5} This finding has been consistent in studies made throughout the country, as is shown in the Children's Bureau Report for 1934 (p. 103),² and the earlier Philadelphia Obstetrical Board studies for the years 1931 and 1933.³ Another way of stating the problem is that deaths following abortion constitute nearly half of all maternal deaths from septicemia,² and that in the District of Columbia report^{4, 5} 36 per cent of all preventable maternal deaths from whatever cause and at whatever stage of pregnancy are due to abortion.

The following is an analysis of abortion deaths in the District occurring in the period from Jan. 1, 1938, through Dec. 31, 1940. The total maternal deaths under twenty weeks of gestation are presented in Table I. In 22 per cent of these cases, death is not due to abortion (Group A). It is reasonable to suppose that future reports will show a decreased incidence in deaths from these causes, since treatment for hyperemesis is improving and the attention of the profession is being drawn to the importance of the early diagnosis of ectopic pregnancy.

In Group B (5 cases, or 7 per cent of the total), death occurred in pregnant women who were suffering from a fatal intercurrent disease. These deaths are not primarily maternal deaths but deaths from various diseases where pregnancy is an associated condition, and the abortions in this group are perhaps the only ones which can be unequivocally labeled as spontaneous.

TABLE I. DEATHS UNDER 20 WEEKS' GESTATION IN DISTRICT OF COLUMBIA MATERNAL MORTALITY STUDY JANUARY, 1938, TO DECEMBER, 1940

		NUMBER	PER CENT
A. Deaths from various causes		17	22
Hyperemesis	3		
Hydatidiform mole	1		
Ectopic pregnancy	13		
B. Deaths following abortions associated with fatal intercurrent disease		5	7
Acute leucemia	1		
Pneumonia	2		
Pyelitis	1		
Rheumatic fever with congestive failure and post-abortion hemorrhage	1		
C. Deaths following abortions		54	71
1. No evidence of induction	10		
2. Induced abortion deaths	44		
Total		76	100

The remaining 54 cases (Group C) comprising 71 per cent of the total deaths occurring in pregnant women up to the twentieth week of gestation are abortion deaths.

Of these 54 cases there were 10, or 18.5 per cent, where we could find no evidence of induction in the medical record or in the autopsy report. A summary of these cases is given in Table II. However, neither could we prove that all ten were spontaneous.

TABLE II. GROUP C. DEATHS FOLLOWING ABORTIONS

		NUMBER	PER CENT
1. No evidence of induction		10	18.5
a. Abortion with degenerating fibroid	1		
b. Out-of-town cases with no history	2		
c. Patient moribund on admission	1		
d. Operative interference and/or numerous vaginal examinations	4		
e. Pregnancy denied	2		
2. Induced abortion deaths		44	81.5
Total		54	100.0

The following case (Group C 1 a), which came under our personal observation, tends to bear out Hamilton's contention that "the incomplete spontaneous abortion offers the same nidus as retained secundines post partum; the uterus recognizes no moral distinctions."²¹

Gallinger Municipal Hospital (No. B4246). B. S., aged 37, colored, married, gravida ii, para 0. History of menorrhagia and metrorrhagia of three months' duration. Admitted Oct. 20, 1939, for hysterectomy. Diagnosis: Fibromyoma uteri. Discharged Oct. 23, 1939, without operation on account of upper respiratory infection. Readmitted Nov. 3, 1939, with history of spontaneous incomplete abortion with bleeding since October 24. Dilatation and curettage on November 5. Septic course ending in death on November 11 in spite of chemotherapy and frequent transfusions.

Pathologic findings: Specimen from dilatation and curettage showed necrotic placenta. Post-mortem findings, 4 cm. necrotic foul-smelling fibroid. Intramural fibroid above internal os.

Diagnosis: Septicemia, acute gangrenous and suppurative myometritis.

Whereas the evidence favors the diagnosis of spontaneous abortion in this case, one cannot be as positive about the other nine.

Although no evidence of induction was found in the history or autopsy of these 9 cases, the records do not differ from those where induction was admitted in the history or was shown by the post-mortem examination.

Perhaps 4 women in this group died because of unwise operative procedures or neglected hemorrhage, but one cannot prove that interference with the pregnancy may not have been attempted first. Laparotomies and the shuttling of patients from one hospital to another occur in cases of admitted induction. Where no evidence of induction exists, the out-of-town patients with no history and those who deny pregnancy are most under suspicion. In the known induced group, the autopsy does not necessarily reveal a recently traumatized cervix in a multipara who has inserted a catheter and more than one woman who claims to have fallen accidentally turns out to have a ruptured uterus or a lacerated internal os at necropsy. Therefore we do not consider that we are going outside the limits of probability in suggesting that at least half of the cases where no evidence of induction was available were actually induced.

Among the 44 deaths (Group C 2) where evidence of induction exists, these constituted 81.5 per cent of the total abortion deaths (Group C), and if we add one-half of the cases from the group just described, we can say that 90 per cent of the abortion deaths in the District of Columbia in the past three years were due to induced abortions.

The major cause of abortion deaths (Table III) is what it has always been, sepsis. In only 3, or 5.6 per cent of the total abortion deaths, sepsis was not the major problem.

Among those who died of septicemia, 3 cases were associated with ectopic pregnancy. It is fair to ask whether the patient would have died in these cases had an induced abortion been attempted in the presence of an intrauterine pregnancy alone, but one may add that had an induced abortion not been attempted at all a diagnosis of ectopic pregnancy might have been more quickly made. Physicians must constantly bear in mind that neither the patient, herself, nor the abortionist are accomplished gynecologists and that more than one abortion is attempted in the presence of extrauterine pregnancy.

Another patient died following a mismatched transfusion, but had she not tried to abort herself she probably would not have needed the transfusion.

TABLE III. CAUSE OF DEATH IN 54 ABORTION CASES

		NUMBER	PER CENT
I. Sepsis		51	94.4
1. No evidence of induction available	10		
2. Induced abortions	41		
a. Sepsis alone	36		
b. Sepsis associated with ectopic pregnancy	3		
c. Sepsis associated with transfusion reaction	1		
d. Sepsis associated with possible poisoning	1		
II. Nonseptic Deaths		3	5.6
Air embolism	2		
Poison	1		
Total		54	100.0

The question sometimes arises as to whether the patient was pregnant at all at the time an abortion was attempted. We know definitely of one such case where no evidence of pregnancy was found by the hospital pathologist post mortem, and it is not accordingly listed as a maternal death. That there may actually be others among the 54 is a fair surmise, as a positive diagnosis of early pregnancy cannot always be made without a microscope, and the coroner's office of the District of Columbia does not give a microscopic report.

Air embolism was given as the cause of death in three pregnant women; only two are listed here, as in the third, pregnancy had progressed beyond the twentieth week. In all three cases the individual was found dead on the premises where abortion had been attempted. An inquest was made in one of these cases. Criminal proceedings followed. A registered nurse pleaded guilty and was sentenced to three years in the penitentiary. The criminal record mentions the use of a catheter but does not go into further details. No inquest was made in the other two cases; they were signed out as "self-induced" by the homicide squad.

This brings up the question of the preventability of these abortion deaths. According to the usual coding of Maternal Mortality Committees, abortion deaths are classified as preventable, the responsibility being assigned to the patient. Our analysis (Table IV) of the medical

TABLE IV. COMPARISON OF MEDICAL AND POLICE RECORDS

SOURCE	MEDICAL RECORD		HOMICIDE SQUAD RECORD	
	NUMBER	PER CENT	NUMBER	PER CENT
Self	17	39	28	64
Second party	12	27	4	9
Unknown	15	34	12	27
Total	44	100	44	100

record of the 44 known induced cases shows that 39 per cent were self-induced and 27 per cent were admittedly performed by a second party.

As far as the last 34 per cent are concerned, we have the post-mortem evidence of perforated uterus, or lacerated internal os, that these abortions were induced, but we do not know by whom, or when and how they were performed. A comparative analysis of the homicide squad records shows that of the total 44 cases, 29 cases, or 63 per cent, were signed out as self-induced abortions. Four persons were brought up before the Grand Jury and only one was convicted. Another conviction was made in the case of a woman where a six months' pregnancy was interrupted, resulting in the premature birth of an infant which lived six days. This case is not included in the total of 44 cases.

Such a record is not an unusual one and should not be taken to reflect discredit on the police or the Courts of the District of Columbia in particular but rather on the American scene in general. Convictions in cases of criminal abortion are few and far between.⁶ Statutes are on the books of every State prescribing punishment for any person who induces an abortion. The law further prescribes that it is the duty of one who knows of a case of criminal abortion to report it to the police. Actually the records of the Narcotic Division of the District of Columbia to whom cases are supposed to be reported show that 79 cases of abortions were reported in the course of two and one-half years, obviously an infinitesimal fraction of the number of cases performed in the District.

During the period from June, 1938, to May, 1941, 12 individuals were brought before the Grand Jury; 7 of these were convicted and sentenced to from one to three years in the penitentiary. The occupations recorded for these abortionists include two physicians, one chiropractor, one registered nurse, four practical nurses, one post-office clerk, one auto mechanic, one forger, and one pharmacist. There were 2 colored and 10 white individuals.

TABLE V. POLICE RECORD, HOMICIDE SQUAD

SELF INDUCED	OUT OF TOWN	NATURAL	NOT KNOWN TO POLICE	TO GRAND JURY		TOTAL
				CONV.	EXON.	
28	7	2	3	1	3	44

The difference between the medical record and the police record (Table IV and Table V) in the assignment of the cause of death reflects the problem known to everyone who has been connected with a criminal abortion case. The abortionist's lawyers are experienced in the tactics of delay; witnesses for the prosecution back out at the last moment; the jury will not find the abortionist guilty for, as a member of the police force told the author, "on any jury you are sure to find that some jurymen's wife has had an abortion performed at some time." In other words, everyone tries to dodge the issue and nothing happens. In one famous case, a physician, aged 65 years, was first arrested in 1929, being rearrested nine times before he was convicted in 1937. In

3 of these cases, the patient on whom he was accused of performing an illegal abortion died. Another doctor, aged 75 years, was found not guilty by the jury in a case involving the death of a young girl in 1939, and has three other indictments pending before the Grand Jury, one of them involving a death. At date of writing he was still out on bail.

SUMMARY AND CONCLUSIONS

1. Fifty-four women died from abortions in the District of Columbia in the period from January, 1938, to December, 1940. This constitutes 24 per cent of the total maternal mortality deaths, or 71 per cent of deaths in pregnant women before the twentieth week of gestation.

2. Ten, or 18.5 per cent, of these 54 cases showed no evidence of induction, but the cases could not be proved to be spontaneous. Death from uncomplicated spontaneous abortion is probably very rare.

3. Forty-four, or 81.4 per cent, of these cases were induced. Thirty-nine per cent were self-induced; in 27 per cent of the cases, the patient admitted outside interference; in the last 34 per cent post-mortem findings were the only evidence of induction.

4. Sepsis was the principal cause of death in all but three cases out of a total of 54.

5. In connection with four of these deaths, one abortionist was tried and found guilty, three others were exonerated.

6. During the period July, 1938, to May, 1941, twelve abortionists were brought before the Grand Jury in the District of Columbia. Seven were convicted. This sampling of abortionists includes two licensed physicians, one forger, one auto mechanic, and one post-office clerk.

The remedy does not lie entirely in a change of the law. The District abortion law is cited by Taussig⁶ as one of the most liberal in the United States, since an abortion is permitted "when necessary to preserve the woman's life or *health* and under the direction of a licensed practitioner of medicine." This provision of the law seems to be taken advantage of only by the unscrupulous abortionist and can be used as an excuse by him in court. Reputable physicians perform abortions only where there is a clear-cut medical reason showing that the mother's life is endangered.

Ideally, of course, no abortion should be performed except in an open hospital under the most careful medical supervision.

Failing this, the following measures, tending to the simultaneous education and policing of the public and community, are suggested:

1. A public health educational campaign on the dangers of abortion, both criminal and self-induced.

2. Education of the public to seek medical treatment immediately following an induced abortion.

3. A concerted effort on the part of the public, the medical profession, the police, and courts to drive the most unskillful operators in a community out of business.

4. Acceptance of responsibility for the treatment of abortion patients by local hospitals instead of shunting these patients from one hospital to another.

5. Vigorous treatment of sepsis by chemotherapy and transfusion with a minimum of manipulation.

I wish to express my appreciation to Dr. Herbert Ramsey, Chairman of the Obstetrical Board of the District of Columbia, to Dr. Oppenheimer of the Department of Health of the District of Columbia, and to the Children's Bureau for permission to study their records; to the Federal Bureau of Investigation; and to the members of the Homicide and Narcotic Squads of the Metropolitan Police of the District of Columbia. The author accepts sole responsibility for the conclusions and recommendations suggested.

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WEIGHT STUDIES IN PREGNANCY

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W EIGHT studies during pregnancy are neither unimportant nor all-important. Primarily, weight determination establishes an indication to the subject's dietary habits and exertive actions and as an augury in certain cases of impending toxemia. Other interpretations of its value are alluded to such as regulation of fetal weight gain, effect upon duration of labor, increase in complications, etc.

The present report, based upon observations in 3,230 women during pregnancy, parturition, and post partum, is rather to interpret factually the findings than to record a mass of data, and then to draw some conclusions on the worth of routine weight taking and the limitations circumscribing its practical applications.

DATA OBTAINED

The usual weight of the patient was taken as the base, unless there had been a sudden weight gain prior to pregnancy. The weight charts

began at the second to the sixth month of pregnancy and records were made at least at monthly intervals until delivery. In the majority and in all toxic patients, weighings were at one- to two-week intervals during the last six weeks of pregnancy. The weight was again noted four to six weeks post partum.

The character of the labor, its duration, the type of pelvis, and dystocia due to bony and soft parts were noted. Complicating factors, notably pregnancy toxemia, were recorded. The change in the patient's weight post partum with respect to her usual weight and pregnancy gain was indicated. The baby's birth weight was registered in each case.

ANALYSIS OF DATA

As will be seen from Tables I to VI-A, the weight charts were first arranged according to age groups, and averages for weight gain, fetal weight, and hours of labor computed for each five-year group from fifteen to forty-five years. This is detailed in Table I.

Table II records the fetal birth weight in mothers gaining from one to sixty pounds in five-pound groups, and Table II-A, those in mothers losing up to 10 pounds throughout a pregnancy.

The duration of labor ratio to pounds gained during pregnancy is recorded in Table III and to weight loss, in Table III-A.

Delivery analysis of weight gain groups is recorded in Table IV and Table IV-A. "Delivery other than normal" includes elective low forceps in these and the succeeding tables and consequent increased incidence is manifest.

TABLE I

3,230 cases	
Average increase in weight	23.2 pounds
Age group from 16 to 20 years	600 cases
a. Average weight increased	24.8 pounds
b. Average fetal weight	7.2 pounds
c. Average duration of labor	15 hours
Age group from 21 to 25 years	1,136 cases
a. Average weight increased	24.5 pounds
b. Average fetal weight	7.4 pounds
c. Average duration of labor	17 hours
Age group from 26 to 30 years	884 cases
a. Average weight increased	23.5 pounds
b. Average fetal weight	7.5 pounds
c. Average duration of labor	17 hours
Age group from 31 to 35 years	425 cases
a. Average weight increased	19.6 pounds
b. Average fetal weight	7.7 pounds
c. Average duration of labor	16.5 hours
Age group from 36 to 40 years	165 cases
a. Average weight increased	16.4 pounds
b. Average fetal weight	7.2 pounds
c. Average duration of labor	13 hours
Age group from 41 to 45 years	20 cases
a. Average weight increased	18 pounds
b. Average fetal weight	7.7 pounds
c. Average duration of labor	11 hours

TABLE II. FETAL WEIGHT RATIO TO WEIGHT GAINED DURING PREGNANCY

POUNDS GAINED	NUMBER OF CASES	FETAL WEIGHT
1-5	51	7.2
6-10	149	7.4
11-15	446	7.3
16-20	648	7.5
21-25	623	7.4
26-30	507	7.3
31-35	329	7.6
36-40	235	7.6
41-45	98	7.8
46-50	42	8.1
51-55	12	7.5
56-60	10	10.5

TABLE II-A. FETAL WEIGHT RATIO TO WEIGHT LOST DURING PREGNANCY

POUNDS LOST	NUMBER OF CASES	FETAL WEIGHT
1-5	53	7.6
6-10	27	7.4

TABLE III. DURATION OF LABOR RATIO TO POUNDS GAINED DURING PREGNANCY

WEIGHT GAIN	NUMBER OF CASES	DURATION OF LABOR (HOURS)
1-5	51	13.5
6-10	149	12.3
11-15	446	14.6
16-20	648	16.0
21-25	623	17.0
26-30	507	17.6
31-35	329	15.5
36-40	235	15.8
41-45	98	17.2
46-50	42	18.8
51-55	12	17.2
56-60	10	28.0

TABLE III-A. DURATION OF LABOR RATIO TO POUNDS LOST DURING PREGNANCY

WEIGHT LOSS	NUMBER OF CASES	DURATION OF LABOR (HOURS)
1-5	53	16.0
6-10	27	10.5

TABLE IV. DELIVERY ANALYSIS OF WEIGHT GAIN GROUPS

POUNDS GAINED	NUMBER CASES	NORMAL DELIVERY	DELIVERIES OTHER THAN NORMAL
1-5	51	45—88.2%	6—11.8%
6-10	149	120—80.6%	29—19.4%
11-15	446	366—82.1%	80—17.9%
16-20	648	496—76.5%	152—23.5%
21-25	623	400—64.2%	223—35.8%
26-30	507	270—53.3%	237—46.7%
31-35	329	196—59.6%	133—40.4%
36-40	235	164—69.8%	71—30.2%
41-45	98	60—61.2%	38—38.8%
46-50	42	30—71.4%	12—28.6%
51-55	12	6—50.0%	6—50.0%
56-60	10	7—70.0%	3—30.0%

The delivery analysis of age groups is given in Table V.

Complications for groups gaining 1 to 60 pounds and losing 1 to 10 are recorded in Tables VI and VI-A.

The incidence of toxemia of pregnancy, mild to severe, including eclampsia, is recorded for the twenty-one to twenty-five age groups,

TABLE IV-A. DELIVERY ANALYSIS OF WEIGHT LOSS GROUPS

POUNDS LOST	NUMBER CASES	NORMAL DELIVERY	DELIVERIES OTHER THAN NORMAL
1-5	53	47	6
6-10	27	25	2

TABLE V

GROUP	NORMAL DELIVERY	ABNORMAL DELIVERY
16-20	426—71%	174—28.0%
21-25	692—61%	444—39.0%
26-30	564—64%	320—36.0%
31-35	342—80%	83—20.0%
36-40	125—75%	40—24.3%
41-45	12—60%	8—40.0%

TABLE VI. COMPLICATIONS IN GROUPS GAINING

GROUP	NO. CASES	COMPLICATIONS	% COMPLICATIONS
1-5	51	7	14.0
6-10	149	42	28.0
11-15	446	51	11.4
16-20	648	67	10.3
21-25	623	59	9.4
26-30	507	81	16.0
31-35	329	77	23.4
36-40	235	39	16.6
41-45	98	16	16.3
46-50	42	19	45.0
51-55	12	3	25.0
56-60	10	4	40.0

TABLE VI-A. COMPLICATIONS IN GROUPS LOSING

GROUP	NO. CASES	COMPLICATIONS
1-5	53	8
6-10	27	4

TABLE VII. INCIDENCE OF TOXEMIA

AGE GROUP	NO. CASES	TOXEMIA CASES	% TOXEMIA
21-25	1,136	67	5.9

TABLE VII-A. INCIDENCE OF TOXEMIA

WEIGHT GROUP	NO. CASES	TOXEMIA CASES	% TOXEMIA
21-25	623	22	3.5
26-30	507	28	5.5
31-35	329	39	11.8
Total	1,459	89	Average 6.1

which is numerically the largest (Table VII). The table also gives the same data for weight groups 21-25, 26-30, and 31-35, which total a comparable number.

DISCUSSION

Something definitive may be said from the data recorded in table form, but there also are some no less important observations not easily portrayable without being involved and confusing. The average weight gained in the 3,230 cases was 23.2 pounds, ranging in the five-year age groups from 16 to 45 from 16.4 to 24.8 pounds. It is of interest that the older groups gained less. It is also true that the average "usual weight" of the older groups was greater, indicating a tendency for those of normal or less than normal weight to gain proportionately more during pregnancy than those who were overweight. It is noted that the fetal weight is not influenced by maternal weight changes (barring one small group gaining 55 to 60 pounds during pregnancy). This is in accord with competent observations on "war babies" and impressions of many years. The average fetal weight for the entire series was 7.4 pounds.

Except for the extreme group of 55 to 60 pounds gain, the duration of labor may be said to be essentially uninfluenced by weight gain. There are notable exceptions to this rule, however, which "averages" do not cover. Patients gaining more than 25 pounds have nearly 10 per cent greater chance of operative delivery than those gaining less, and the hazards of anesthesia and perineal infection are considerably greater.

In the analysis by age groups, the incidence of normal delivery indicates a higher percentage of normal delivery in the older (and multiparous) age ranges. However, while the older age groups had higher *normal delivery* ratings, they also had higher percentages of complications, as also indicated in Table VI of the weight groups. But a young primipara of normal weight gain (23.2 pounds) is a better prospect than a multipara of any age who has gained excessively.

Since excessive weight gain is commonly believed to be associated with or conducive to toxemia of pregnancy, Tables VII and VII-A are of more than ordinary interest. Private observations of a large number of these patients likewise permits some latitude in the interpretation of the findings. The numerically largest age group (twenty-one to twenty-five) had a toxemia incidence of 5.9 per cent. In the weight groups of 21 to 25 pounds, the incidence was 3.5 per cent; 26 to 30 pounds, 5.5 per cent; while from 31 to 35 pounds it rose sharply to 11.8 per cent. Casual translation of these data might lead one to believe that weight gain per se was of vital importance in causing or preceding toxemia. A moderately capacious experience will recall many patients with toxemia of varying severity with no excessive (or even less than normal) weight

gains. And the vast majority of those who gain excessively do not become toxemic. The consequence of this is not negated by the data given in Table VII-A. Recollection of patients rather than figures recalls three more or less distinct groups gaining excessively; namely, those with considerable edema, mostly static; those "bloated" patients with minimal pitting edema but obvious increase in body fluids; and those whose weight gain is largely due to tissue gain. Thus some patients are obviously hydropic without having or developing toxemia, while others with "occult edema" either increasing interstitial fluid with no static accumulations or undergoing hygroplasmic changes in their protoplasm, are more likely subjects. A *sensation* of swollen hands or face thus assumes greater importance than pitting edema in patients gaining weight. And in the matter of evenness of weight gain those patients developing toxemia did not begin to gain rapidly until the characteristic loss of fluid balancing power shared by most toxemic patients had become evident. In other words, excessive fluid accumulation, generally but not always present in toxemic patients, is a concomitant factor in toxemia development, a symptom as it were of the complex itself. It suggests an increased incidence of toxemia, more especially in those patients with "occult edema" showing moderate upward fluctuations in blood pressure. And it is this group in the early stages who respond best to dehydration therapy.

Among those whose excessive weight gain is mostly stereoplasm it is our belief that toxemia incidence is not increased.

The post-partum weight loss is dependent upon the amount and type of weight gain, the hydropic gainers returning to or below their usual weight within two weeks of parturition, while the tissue gainers are likely to retain most of the weight gained in excess of the normal increment. Roughly, in the latter group it may be said that patients will retain beyond six weeks 60 to 80 per cent of all weight gained in excess of 22 pounds. In patients with either static or occult edema, no such calculation is permissible, inasmuch as the causative factors in the first and the control of fluid balance in the second produce a rapid water loss within a few days of delivery.

Since all of the patients were cautioned to limit weight gain in pregnancy to 20 to 25 pounds, a mild lowering of the general average weight has been effected.

The increment by trimesters is of some interest. There is generally little gain in the first three months, although glaring exceptions may be observed when a huge appetite substitutes for the more commonly observed nausea and vomiting of pregnancy. The majority fall into the following categories:

- First 3 months. 2 to 3 pounds gain
- Second 3 months, 8 pounds gain
- Third 3 months. 12 pounds gain

SUMMARY

Analysis of weight data of 3,230 patients indicates an average maternal weight gain of 23.2 pounds and a fetal weight gain of 7.4 pounds. The baby's birth weight is not related to maternal weight gain or loss unless the patient is diabetic or the gain excessive.

Post-partum weight loss is within 5 pounds of the total gain for all patients who gained the average poundage. But with excessive weight gain, 60 to 80 per cent of the weight gain in excess of normal will be retained, except in hydropic patients.

In general, it may be said that the amount of weight gained has relatively little effect upon the duration of labor, although excessive weight gain definitely increases the number of complications.

Weight gain per se is of little significance in the consideration of toxemia unless the weight gain is typed. The vast majority of all patients gaining an abnormal amount do not become toxemic. However, the toxemia incidence definitely rises as weight gain in excess of normal appears. Differentiation of hydropic from stereoplastic weight gain is of more value. For it is in the "edema group" (and most notably where edema is occult or nonstatic in type) that the incidence of toxemia is increased. Practically, however, sharp differentiation of the two is not always simple, and may depend upon clinical response to dehydration therapy in suspected weight gainers. Calculations of fluid retention, based upon fluid intake and urine output is of added value in deciding how to type such patients, to further the prognostic worth of weight observation.

39 GIFFORD AVENUE

Young, William C.: *Observations and Experiments on Mating Behavior in Female Mammals*, Quart. Rev. Biol. 16: 311, 1941.

Extensive data on the behavior displayed at the time of estrus are now available for the rat, guinea pig, rabbit, sheep, cattle, pig, horse, cat, dog, howler, rhesus monkey and chimpanzee.

The generalization is warranted that each species displays a characteristic pattern of behavior with considerable individual variations. The latter are greatest among infrahuman primates.

In the mammals studied, estrous behavior has an endocrine basis. It is abolished by removal of the ovaries and restored by suitable replacement therapy. Ovarian action seems mediated by a neural center, or centers, in the hypothalamus or even farther back in the mesencephalon. Undoubtedly also additional physiologic factors are involved, social and environmental, in members of higher orders. Individual differences, that are a matter of age, or differences that may be of genetic origin, determine greatly the nature of the response.

HUGO EHRENFEST.

ADDITIONAL OBSERVATIONS ON MATERNAL PULMONARY EMBOLISM BY AMNIOTIC FLUID

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FATAL maternal pulmonary embolism by amniotic fluid and its particulate contents was described recently by the authors as a cause of obstetric shock and of other sudden deaths in, or following, parturition.¹ Clinically, the disease was characterized by profound shock which led in some cases to pulmonary edema, and in others was accompanied by uterine atony and hemorrhage. The essential pathology was found on microscopic examination of the lungs. It consisted of widespread embolism of small pulmonary arteries, arterioles, and capillaries by the particulate matter found in amniotic fluid and meconium. The disease was duplicated clinically and pathologically in dogs and rabbits by the intravenous injection of those substances obtained from human beings.

While that communication was in press, two additional obstetric deaths were found to be complicated by this form of embolism. Since they contain several features not seen in the 8 cases previously reported, they are presented here. These additions are (a) the subsequent fate of the emboli in women, (b) the sublethal form of this condition, (c) lanugo hair as embolus, and (d) such embolism in the absence of labor contractions.

CASE 1.—E. McL., white, 35 years old, para i, gravida ii, was a patient of Dr. Eloise Parsons at the Illinois Central Hospital, Chicago. She died seven days after delivery of a stillborn, full-term infant. Labor lasted about four hours, the second stage being twenty-five minutes and the third stage ten minutes. Subjective and visible labor pains were never strong, but she developed terrific pain in her right shoulder, became listless and the abdomen became sensitive early in the first stage. After delivery, which was accompanied by no excess hemorrhage, and was aided by low forceps, the patient was pale and continued to complain of pain in her shoulders and was nauseated and vomited several times. She received several blood transfusions, but her abdomen enlarged and a tender growing mass appeared in the right lower quadrant. She developed twitchings of the hands and generalized convulsions and died. The final clinical diagnosis was possible abdominal malignancy.

Post-mortem Findings.—Necropsy disclosed about 4,000 c.c. of bloody fluid and dark bloody clots in the peritoneal cavity. This seemed to have had its origin from a 3 cm. sized laceration through the left posterior uterine isthmus, the laceration involving the left uterine plexus.

There were no other important gross pathologic changes. The lungs together weighed 659 Gm. and grossly showed only a slight congestion. The heart weighed 250 Gm. The right ventricle was not dilated; the left was in systole. The abdominal organs were pale but not exsanguinated.

Histopathology.—Lungs: The principal pathologic findings were in small arteries, arterioles, and capillaries, many of which were occluded by masses of bluish-staining stringy material resembling mucin, or by an amorphous pink-staining substance, and occasionally by crescentic squamallike bodies. These materials were heavily infiltrated by large



Fig. 1.—Pulmonary embolus of mucus and amorphous debris seven days after inception. Note macrophage and leucocyte reaction (Case 1). $\times 165$.

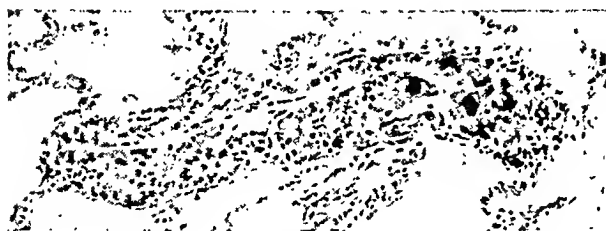


Fig. 2.



Fig. 3.

Fig. 2.—Mononuclear and multinuclear giant cells reacting to an embolus in an arteriole seven days after embolization (Case 1). $\times 165$.

Fig. 3.—Panarteritis resulting from reaction to an embolus in small arteriole seven days after parturition (Case 1). $\times 165$.

mononuclear macrophages, neutrophilic and eosinophilic polymorphonuclear leucocytes, and lymphocyte-like cells (Fig. 1). In some vessels there were in addition many mononuclear and multinuclear giant cells (Fig. 2). The cellular infiltration into some of the smaller emboli almost obscured them (Fig. 3). A refractile cylindrical body was seen occluding one vessel. Two giant cells were at one end of the structure. It contained some pigment granules and was similar in every respect to lanugo hair (Fig. 4). The inflammatory reaction sometimes involved the vessel wall and the adjacent lung tissue. The amount of embolism was moderate in comparison with that in the cases previously reported.

In addition, the lungs showed considerable emphysema and numerous megakaryocyte-like type of giant cell. There was no pneumonia or edema, but some acute hyperemia.

Uterine veins: A section through the region of the laceration in the left posterior segment of the uterine isthmus and the adjacent uterine plexus showed thrombosis of the blood vessels and hemorrhage into the areolar tissue. Some of the thrombi contained epithelial squamas, and showed beginning organization, as did the interstitial blood. Also located in the areolar tissue, as well as on the peritoneal surface and

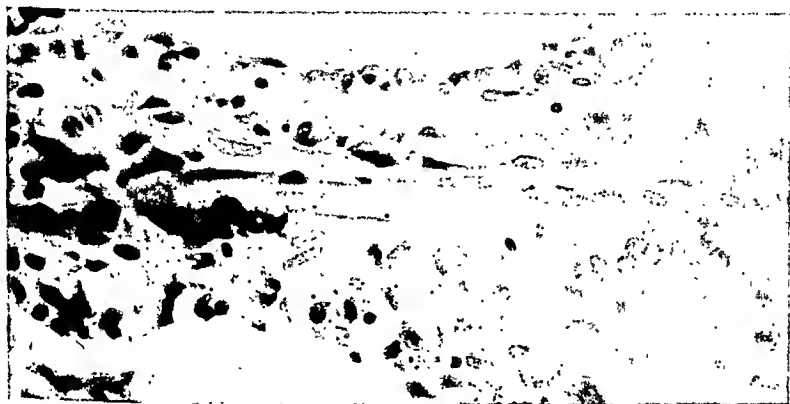


Fig. 4.—A lanugo hair seen as an embolus in an arteriole. Note giant cell reaction (Case 1). $\times 525$.

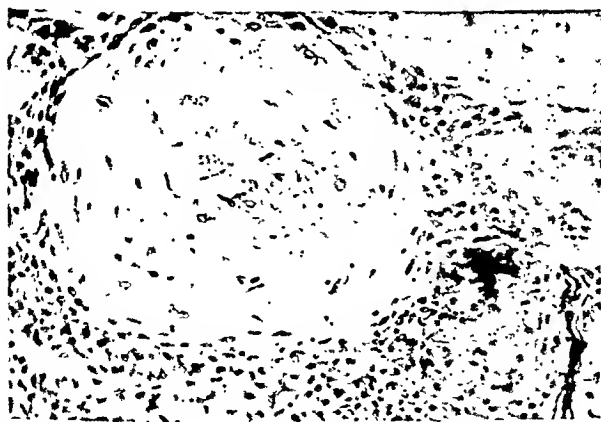


Fig. 5.—Small artery of omentum with cuff of decidual cells. Note sheet of squamas in lower right corner (Case 1). $\times 220$.

directly in the laceration, were many similar squamas together with much mucuslike material. To these foreign substances there was an intense acute inflammatory reaction.

Omentum: A section through the omentum showed foreign bodies similar to those seen in the pulmonary and uterine vessels described above. There was an intense acute inflammatory reaction to them and to the free blood. In addition the capillaries and arteries were surrounded by a thick cuff of decidual cells (Fig. 5).

Miscellaneous: Liver and kidney sections were not remarkable. Sections of the brain showed small disseminated, sharply circumscribed foci of gliosis and one area of demyelination.

Final Pathologic Diagnosis.—Massive intraperitoneal hemorrhage from rupture of the uterus. Pulmonary embolism by amniotic fluid. Multiple sclerosis.

CASE 2.—M. D., white, 38 years old, para ii, gravida iv, was a patient at the Chicago Lying-in Hospital. Because of a persistent hypertension which was not alleviated by treatment, she was admitted to the hospital

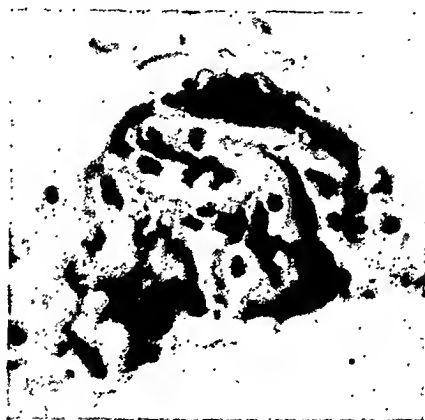


Fig. 6.—Squamas occluding an arteriole (Case 2). $\times 450$.

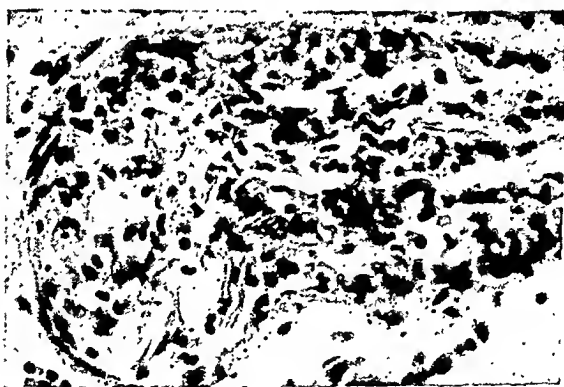


Fig. 7.—Mucus and squamas with leucocytic reaction occluding a small artery (Case 2). $\times 450$.

near term. Her blood pressure ranged from 120-170/70-120. Her urine had slight traces of albumin. The quantitative albumin was 0.09 Gm./24 hr. specimen. Attempts at a medical induction were unsuccessful. Two days later painless bleeding occurred and examination revealed an anterior-lying total placenta previa for which a laparotrachelotomy was performed under local anesthesia. It was necessary to put the operating hand through the placenta and do a version and extraction with forceps on the aftercoming head of a living baby.

Following the operation the blood pressure and pulse were not obtainable. The patient was very pallid. Her breathing became gasping. She was given 500 c.c. of 20 per cent glucose, 500 c.c. of physiologic

saline, two blood transfusions, totaling 1,100 c.c., oxygen, and stimulants. The patient remained in shock. Pressure on the uterus, which had been packed, evacuated about 200 c.c. of blood and clots. She died about three and one-half hours after the operation began. The estimated blood loss was 800 c.c.

The final clinical impression was total placenta previa, toxemia, and laparotrachelotomy with hemorrhage.

Post-mortem Examination.—There was pallor of the skin and all abdominal organs. Both lower lobes of the lungs were atelectatic. The uterus was contracted. The operative incision was closed adequately. There was moderate pulmonary edema and hyperemia (lungs together weighed 600 Gm.). The left ventricle of the heart was contracted, but the right ventricle was remarkably flabby.

Histopathology.—Lungs: A few small arteries, arterioles, and capillaries showed occlusion by emboli which consisted of epithelial squamas and mucus (Figs. 6 and 7). There was an admixture of leucocytes in some of the mucus, and other vessels also showed a great excess of leucocytes. The total amount of embolism was small compared with the nine preceding cases.

The lungs in addition showed much emphysema, some edema, and focal atelectasis.

Miscellaneous: Kidneys: Sections showed some parenchymatous change. The glomerular tufts showed thickening of the endothelium. They were large and filled Bowman's space. Liver: Sections showed no abnormalities.

Final Pathologic Diagnosis.—Postoperative state following laparotrachelotomy for placenta previa. Toxemia of pregnancy (?). Minimal pulmonary embolism by amniotic fluid. Questionable exsanguination.

DISCUSSION

In neither of these two cases was there the picture of profound, sudden shock which was described in the previous paper. This is in accordance with the amount of embolism which was seen on microscopic examination of the lungs. In both of these two women, this was less than in the previous eight cases. In Case 1, the effects of the embolism appear to have been subclinical or masked by the symptoms due to the ruptured uterus. In Case 2 death appears to have been due to vasomotor collapse in which the relative importance of hemorrhage, operative trauma, pulmonary embolism, and possibly nonconvulsive toxemia cannot be determined in retrospect. This case, then, may illustrate the point previously made that the effects of this form of embolism may be obscured by a combination of causes, and that these might lead to death, whereas each alone might be survived.

Case 2 illustrates that embolism of the lungs by the particulate materials in amniotic fluid can occur in the absence of labor pains if a route is provided by other means, in this case, incision through the placental site. However, since the amount of embolism seen in this case was distinctly less than that in the other nine cases, it tends to fortify our opinion that strong or excessive labor pains are an important predisposing factor.

In our previous paper we made considerable efforts to determine the origin of the emboli materials found in the lungs. We concluded that the emboli represented the epithelial squamas and vernix caseosa found in the amniotic fluid together with the meconium present there in some cases. The presence of lanugo hair, as an embolus (Fig. 4), further supports this view.

The large amount of decidual reaction present in the omentum in Case 1 in the presence of intraperitoneal amniotic fluid raises the question of its etiology. Such reactions have been described by Williams,² Harbitz,³ and others. It is the subject of further investigation.

The reaction to the pulmonary embolic materials at seven days was less severe than we had anticipated following our observations on dogs. In these experiments, however, the amniotic fluid and meconium used to embolize the lungs had not been kept sterile, and bacterial infection might, therefore, be responsible for part of the intense reaction illustrated at seven days in our previous paper. The type and amount of macrophage reaction indicates that these materials act approximately like many other aseptic foreign bodies, and that their subsequent fate would probably be complete removal. The mucus was already difficult to identify as such as seven days. The reaction to it was mainly that of macrophages. The squamas and amorphous materials caused a marked foreign body giant cell reaction.

SUMMARY

Two additional cases of maternal pulmonary embolism by amniotic fluid are presented. Lanugo hair is illustrated as a component of the embolic material. Existence of the sublethal form of this condition is shown and the subsequent fate of the human emboli is found to be approximately similar to that described by us in experimental animals. The occurrence of this phenomenon following laparotrachelotomy in the absence of labor contractions is reported.

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By means of a photograph of the five babies and of the official birth certificate made out by the attending physician, another instance of quintuplets is placed on record. The five children were all boys, one of them stillborn, the other four dying soon after birth. Their aggregate weight was ten pounds two ounces, and the birth certificate stated that there was but one placenta.

HUGO EHRENFEST.

THE EFFECT OF NICOTINE ON LACTATION IN WHITE MICE

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STUDY of the hormone levels during pregnancy and the puerperium suggests an endocrine control of lactation. While this supposition may be true, there are other factors, the blood and nerve supplies to the gland, which play an important part in determining the ability of the breast to function adequately.

In the quiescent state, the blood flow through the gland is sufficient to maintain normal tissue metabolism. Prior to the onset of lactation there is a marked vascular engorgement of the breasts; this increased blood flow continues, but is somewhat less pronounced, during the period of secretory activity. Since the synthesis of milk is dependent upon the materials provided by the blood stream, an increased blood flow through the gland is necessary for the maintenance of lactation and conversely a diminution in the blood flow might compromise the secretory activity of that structure. Although the action of nicotine on the blood vessels of the breast has not been subjected to specific study, it is assumed that the vascular effects are the same as noted in other parts of the body, that is, a peripheral vasoconstriction with a diminution of blood flow and a drop in surface temperature.¹⁻³

In the human being, the nerves supplying the breast come from the fourth, fifth, and sixth intercostals; the accompanying sympathetic fibers pass by way of the grey rami communicantes from the thoracic portion of the sympathetic system to plexuses upon the basement membrane about the alveoli. Nerve endings have been demonstrated between the secretory cells in the gland. Although nerve control of lactation has not been confirmed, it is possible that some influence may be exerted through these pathways, since secretion in other glands is a direct result of nervous impulses. Nicotine acts on the ganglia of the secretory nerves, its action consisting of an initial stimulation followed by complete paralysis and cessation of secretion.⁷ This effect has been demonstrated on the salivary, sweat, mucus, and adrenal glands both by local and general administration of the drug.

Any inadequacy of milk production in human beings may be compensated for by the substitution of an artificial formula. In animals, however, the inability of the mother to secrete enough milk to provide for the demands of the litter will evidence itself either in death of the weaker young or in undernutrition of the whole group.

A few attempts have been made to determine the effects of the administration of nicotine on lactation and animal growth.

Behrend and Thienes⁴ and Thienes⁵ have shown that large doses of nicotine given to young animals which are adequately nourished have no effect on subsequent growth and development. Essenberg, Schwind and Patras⁶ gave nicotine to pregnant rats by several methods and found that two-thirds of the young were underweight and that many entire litters were lost by death, abortion, or resorption of the fetuses. Their use, however, of doses large enough to produce convulsions in the animals studied naturally confuses the results, since the fetuses may have been actually poisoned by the drug.

This study was undertaken in an effort to demonstrate the effects of the administration of nicotine on milk production as evidenced by the weight gains in a standard-sized litter of offspring, during a two and one-half weeks' period of lactation. Thirty-six pairs of immature white mice from our laboratory stock were selected for the study and were followed through three consecutive litters.

The average daily water intake of the animals was measured over a period of one week before the experiments were started. The nicotine was then supplied to the animals in the drinking water in a solution of a strength to furnish 0.5, 1.0, or 2.0 mg. in the daily fluid intake. Although the amounts of the drug ingested undoubtedly varied from day to day, the average intake over the period the animals were followed approximated the anticipated amount, since checks on the daily fluid intake revealed it to be at an almost constant level. Other methods of administration of the drug, by injection or the use of cigarette smoke, were considered. Both were eliminated in favor of the one utilized, because nicotine is absorbed readily from the gastrointestinal tract and frequent ingestion of small quantities would maintain a more constant supply in the tissues. Other factors concerned in the choice were the ease of administration and the fact that a much larger daily dose could be utilized.

Of the 36 pairs of mice studied, 12 pairs were used as controls and were given tap water; 10 pairs, 0.5 mg.; 8 pairs, 1.0 mg.; and 6 pairs, 2.0 mg. of nicotine daily. The litters were reduced arbitrarily to six on the day of birth and each group was weighed at birth, at one week, at two weeks, and at two and one-half weeks of age, and the average individual weight obtained. An accurate account of the initial litter size and the ultimate mortality of the offspring was recorded.

RESULTS

Litter Size.—The average number of offspring in each litter was reduced slightly in the groups to which the drug was administered. The largest litters were born to the control animals and to those receiving 0.5 mg. of the drug, and the smallest to those receiving 2.0 mg. daily.

Since the litter size consistently decreased in the animals to which the larger doses of the drug were given, the change probably may be interpreted as the result of the effects of the nicotine. Although the reduction was definite and occurred in each litter in the groups receiving nicotine, a larger series might alter the figures. (Table I).

TABLE I. INITIAL LITTER SIZE

GROUP	AVERAGE NUMBER OF OFFSPRING PER LITTER		
	LITTER 1	LITTER 2	LITTER 3
Control	9.0	11.2	10.4
0.5 mg.	9.4	10.9	10.5
1.0 mg.	8.8	9.0	9.0
2.0 mg.	7.0	8.0	8.0

Mortality.—The mortality rate was high for all groups. This may have been due to the trauma occurring with the removal of the young from the nests on the day of birth for weighing and reduction of the litter size. Although great care was taken, injury may have occurred in some instances. The figures (Table II) reveal a marked variation in

TABLE II. MORTALITY OF OFFSPRING

GROUP	MORTALITY RATE PER LITTER		
	LITTER 1	LITTER 2	LITTER 3
Control	34.5%	27.8%	31.0%
0.5 mg.	33.7%	46.2%	31.6%
1.0 mg.	33.0%	8.3%	46.4%
2.0 mg.	22.5%	16.6%	6.7%

the death of the young with no apparent regard to the amount of the drug ingested. Although the mortality is high, the variation is not inconsistent with the death rates seen in normal groups of untreated mice. The facts that the lowest average mortality in this series occurred in one group of the animals receiving the most drug and that the control group showed a consistently high death rate suggest that factors other than the nicotine played a large part in the loss of the young.

Weight.—The weights of the offspring at birth (Table III) were almost identical for each of the four groups studied, indicating that the administration of the drug in doses below a severely toxic level has no effect on the intrauterine development of the fetuses.

TABLE III. BIRTH WEIGHT

GROUP	AVERAGE BIRTH WEIGHT (GRAMS)		
	LITTER 1	LITTER 2	LITTER 3
Control	1.4	1.35	1.5
0.5 mg.	1.3	1.4	1.25
1.0 mg.	1.4	1.5	1.5
2.0 mg.	1.5	1.4	1.4

The weight curves for each litter of the four groups demonstrate a fairly normal and constant gain. In the first litter (Fig. 1), the offspring from the animals taking 1.0 and 2.0 mg. of nicotine daily weighed

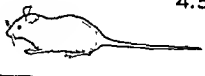











	1 WEEK	2 WEEKS	2½ WEEKS
CONTROL	 4.5	 6.2	 7.9
0.5 MG	 4.7	 7.3	 8.2
1.0 MG	 2.7	 4.0	 4.6
2.0 MG	 3.3	 4.8	 5.1

Fig. 1.—Litter 1. Average individual weight (Gm.).





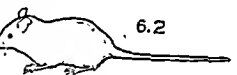


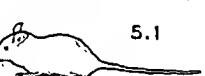


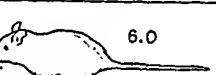
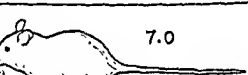
	1 WEEK	2 WEEKS	2½ WEEKS
CONTROL	 3.5	 5.7	 6.5
0.5 MG.	 4.0	 6.2	 6.6
1.0 MG.	 3.9	 5.1	 5.8
2.0 MG.	 4.8	 6.0	 7.0

Fig. 2.—Litter 2. Average individual weight (Gm.).




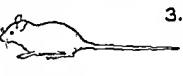
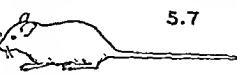

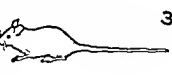





	1 WEEK	2 WEEKS	2½ WEEKS
CONTROL	 3.5	 5.4	 5.5
0.5 MG.	 3.5	 5.7	 6.1
1.0 MG.	 3.1	 5.2	 4.7
2.0 MG.	 4.8	 5.9	 7.1

Fig. 3.—Litter 3. Average individual weight (Gm.).

less than those getting 0.5 mg. of the drug or only water. That this difference was not an effect of the drug is shown by the weights in the second litter (Fig. 2); the offspring of all the groups except those to which 1.0 mg. was given weighed about the same. In the third litter (Fig. 3), the young from the parents receiving nicotine in daily doses of 0.5 and 2.0 mg. outgained the rest. Again as in the previous two litters, those getting 1.0 mg. produced the lightest offspring.

DISCUSSION

Since it has been demonstrated that the administration of nicotine to young normal animals has no effect on their rate of growth and development⁴⁻⁵ any changes produced when the drug is given to the parents must be on the basis of alteration of the milk supply rather than by the nicotine excreted in the milk. The fact, shown in this study, that the weights at birth of offspring of mice being given relatively large doses of nicotine are the same as those of the controls indicates that the nicotine has little or no effect on the intrauterine development of the animals.

The difference in weight curves in the first litter is not very significant since this difference is observed commonly in groups of normal animals at the onset of their reproductive careers. In the second and third litters, two groups of the treated animals showed gains greater than those of the control group, suggesting that in this particular test animal nicotine has little effect on the amount or quality of the milk produced. The group to which 1.0 mg. of the drug was given consistently produced lighter offspring than the other groups. Since the ability to lactate varies considerably with individuals, this observation must be interpreted as a physiologic variation rather than inhibition of lactation by nicotine.

At no time was any alteration in behavior noted. The young were cared for normally in all instances and there was no obvious increase in cannibalism in the nicotine-treated animals as occurred in the groups studied by Essenberg, Schwind, and Patras.⁶

CONCLUSIONS

1. The effect of nicotine on lactation as evidenced by the weight gains in the offspring was studied in white mice. The animals were treated with 0.5, 1.0, or 2.0 mg. of the drug daily through three consecutive litters.
2. A slight but consistent reduction in litter size was noted with increasing doses of the drug.
3. No remarkable differences in mortality rate, birth weight, or weight gain during the period of lactation could be demonstrated between the controls and the treated animals.
4. A marked variation in all the above factors was noted within each individual group.

5. The ingestion of nicotine results in no impairment of lactation in white mice.

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PARALDEHYDE IN OBSTETRICS, WITH PARTICULAR REFERENCE TO ITS USE IN ECLAMPSIA*

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IN 1934 we began to use paraldehyde at the University Hospital as an analgesic in labor and found it to be quite satisfactory. After a period of trial with the rectal route, which had its obvious disadvantages, we started oral administration and here the results were even better. In 1938 we published a report of 350 cases and in it stated that, in our opinion, paraldehyde was the safest and most satisfactory analgesic available at that time.

Since the publication of this report we have continued to use this drug. In the large majority of the cases it is given by mouth and mixed with aromatic elixir to partially disguise the taste. Other clinics are using fruit juices, water or some other medium and one seems to be about as satisfactory as another. It would appear to be important that the mixture should be thoroughly chilled and swallowed quickly, in order to lessen the disagreeable taste and prevent vomiting. Should the latter occur, a second dose given some fifteen minutes later is usually retained and the desired effect results.

It has continued to be our custom to precede paraldehyde by a small dose of one of the barbiturates (e.g., pentobarbital sodium, gr. 3), and we feel that the action of the drug is enhanced somewhat thereby. On the other hand, this is not an inflexible rule, and is not followed in all clinics, some physicians feeling that there is an increase in fatal asphyxia when the combination is used. While our experience does not bear this out, we believe that the point is quite minor and not worthy of any discussion.

*Read at a meeting of the Obstetrical and Gynecological Section of the Baltimore City Medical Society, October 10, 1941.

The time of administration of paraldehyde varies in different clinics, it being our custom to give it when the patient feels that she wants relief. Should she be of the type who demands or expects analgesia from the onset of pain, her request is not answered until labor is well established, for it is in these cases that we find that the duration of labor is sometimes prolonged.

While not constant, the usual initial dose of paraldehyde is 5 or 6 drams in an equal amount of aromatic elixir. Good effect should occur within fifteen minutes and maximum in one-half hour. Duration is about six hours, and the original or a smaller dose may be given at this time if needed. In those patients in whom the drug is given by rectum, the dose is larger, 8 drams of paraldehyde in 5 or 6 drams of mineral or olive oil being used. Here, the effect is slower, one hour being required for maximum effect, and the duration is about the same. Again, repeat doses are quite permissible.

The effect of paraldehyde varies somewhat. The majority of the patients fall into a deep sleep with continuation of their labor. They are usually moderately restless with pains and quiet in the intervals. A few are more restless, roll from side to side and would probably fall out of bed without some preventive, such as bed sides. In another group there appears to be little or no loss of consciousness nor relief from pain, and the drug would seem to have failed entirely, yet later it is found that the patient has no recollection at all of anything that happened after she received it. And finally, in about 5 per cent of the cases the method fails to produce either amnesia or analgesia. One of the major contributing factors to failure is a full stomach, labor having started shortly after the ingestion of a full meal and having progressed rapidly. The greater number of these patients have a very short labor, and the need for relief is not great.

The analgesia seldom reaches the point of surgical anesthesia, so that while spontaneous delivery is satisfactorily carried out and while the incidence of operative delivery is not increased, should the latter be decided upon, some additional method of pain relief is needed. Paraldehyde does not prohibit the use of any of the general anesthetics, indeed the amount needed for complete anesthesia is less than without it. Or, should it be desired to complete the delivery under local or regional anesthesia, this can also be done without added risk.

Effects other than those noted above are not many. The pulse rate is almost routinely increased, but not alarmingly so. Paraldehyde is an extremely safe drug, and we have not had a maternal death, or major accident which could in any way be attributed to it.

From the standpoint of the infant, it is probably safer than any other drug used. While paraldehyde can often be detected upon the baby's breath, most cry spontaneously and any depressing effect dis-

appears rapidly. Resuscitation, when required, is easy and recovery complete. The one exception to this would appear to be the quite premature infant, weak and sickly at best and ill equipped to withstand strain of any kind. In this group the incidence of severe asphyxia is somewhat, though not greatly, increased.

There is another use for paraldehyde in obstetrics that is mentioned at times, but has never been greatly emphasized. This is as a means of producing sedation in eclampsia and pre-eclampsia. To us, this is most important and has not received the attention it deserves. In pre-eclampsia, paraldehyde will quiet the patient more satisfactorily than any sedative used today, and will permit of time to establish whatever routine treatment is desired. Or, should she be in labor, this may continue to termination under its influence without fear of the onset of convulsions. It must be understood that, for this result, the patient must be kept very well sedated and the physician must not hesitate to repeat the drug as often as necessary. Large doses are tolerated very well, and are often required.

It is in the field of eclampsia itself, however, with frequent convulsions, that the value of paraldehyde stands out so prominently. In reading the literature on the treatment of eclampsia, it is found that practically every writer today advocates the conservative method; yet, it is almost invariably stated that should it be impossible to control convulsions by whatever method of sedation is recommended, this form of therapy should be abandoned and operative delivery undertaken. It is stated that this definitely increases the risk and raises maternal mortality, but that a continuation of an unsuccessful type of treatment would give worse results. All of this is quite evident and would need no comment except for the fact that it is our experience that *paraldehyde, in sufficient dosage and repeated often enough, will, without exception, prevent convulsions, keep the patient quiet, and lower the blood pressure.* This last effect, the lowering of the blood pressure, is not outstanding, but there is usually a drop of some 40 to 50 mg. hg, both systolic and diastolic. The pressure has a tendency to remain at the new level for several hours, and then to rise rather gradually. All of this is accomplished with a minimum of risk to both mother and baby.

In 1936 we began to use paraldehyde as the main sedative agent in the treatment of eclampsia, and as time has elapsed have depended more and more upon it for this effect. Our results on the whole have been so encouraging that it was felt that they should be reported although the total number of cases (48) is small.

It must be understood that we are not attempting here to give the treatment of eclampsia, but merely to emphasize the advantages of paraldehyde to produce sedation when this is desired.

The routine followed in all cases is to give paraldehyde rectally in an initial dose of 10 drams in 5 or 6 drams of olive or mineral oil as soon after admission as possible and then to start intravenous concentrated glucose and other therapy. The rectal route is forced upon us by the fact that these patients are unconscious and unable to swallow. The oral would be preferable because of the more rapid absorption and ease of administration. The patients are watched constantly, blood pressures being taken every one-fourth to one-half hour and if restlessness is returning as the effects of the paraldehyde wear off, the dose is repeated. This is continued until the acute stage has passed and the patient is quiet or conscious without the drug. No attempt is made to induce labor in the ante-partum group until danger of convulsions is past, but if the patient is in labor or if labor begins, it is allowed to continue as normally as possible, only absolutely indicated operative work being done and this invariably without inhalation anesthesia. In this series the majority of the patients either were in labor on admission or went into labor spontaneously; however, five recovered from the acute attack, became conscious and rational, but continued to show marked evidences of toxemia, as manifested by hypertension and urinary findings. These we classified as post eclampsia, in contrast to pre-eclampsia, and in this group the uterus was emptied in what seemed the most conservative manner. There seems to be no precedent for the term "post eclampsia," but the need of some designation is evident. The patient no longer has eclampsia; however, she continues to have a toxemia, and is far from complete recovery.

For purposes of comparison we have tabulated 49 consecutive cases of eclampsia which received no paraldehyde but were in other respects treated about the same. The two series are quite comparable in that in each there were 15 cases classified as severe eclampsia, in the paraldehyde group 20 were moderately severe and 13 mild, in the nonparaldehyde these figures were 26 and 8, respectively; and there was also little difference in the time of onset, in the first instance (paraldehyde) 24 were ante partum, 13 intra partum, 10 post partum, and 1 both intra and post partum. In the second series these figures were 21, 15, 12 and 1.

It is when we begin to compare results that the great differences are noted.

In the nonparaldehyde group, 32 of the 49 patients, almost two-thirds, continued to have convulsions in spite of vigorous sedation with the accepted drugs. The number of convulsions after beginning treatment were usually between 1 and 10, one patient having 23 and another 49. The greatest number of convulsions before treatment was started in this group was 9. Comparing these figures with those patients treated with paraldehyde, we find these interesting facts: When we first began to use the drug we were prone to give too small an initial dose and to

delay repeating it as early as it should be repeated. In this group of 22 patients there were 6 who had either one or two convulsions after sedation was begun, about one-fourth as compared to two-thirds in the non-paraldehyde group. The remaining 26 patients received an adequate amount of paraldehyde, and in this group the percentage of failure was zero, no convulsions occurring after sedation had been obtained. Included in this group we find that one patient had 12, one 16, while a third had 28 convulsions before receiving paraldehyde and none after. The amount of the drug necessary to control the convulsions varied from a minimum of 12 to 15 drams to a maximum of 120 drams in one case and 131 drams in another, both over a period of three to four days. As an interesting side light, the latter patient went into labor after some four to five days of treatment and delivered herself of a premature living child. Both mother and baby did well and were discharged from the hospital in good condition some two weeks post partum. At the time of writing this report, she is again a patient of ours, having passed through this second pregnancy with no evidence of toxemia and delivering at term without incident. Both babies are alive and well.

It is our feeling, therefore, that paraldehyde, in sufficient amounts, will absolutely control the convulsions of eclampsia and permit of a continuation of the conservative treatment for an indefinite period of time, whether this be hours or days.

The maternal mortality in the nonparaldehyde group was 7, or 14.29 per cent, and in the second group there was one death, or a 2.08 per cent mortality, this death occurring from bronchopneumonia several days after delivery and recovery from the eclampsia.

Fetal mortality in the nonparaldehyde group was 14, or 28.58 per cent, and in the other 11, or 22.95 per cent, in both instances the figures being uncorrected. These figures would seem to indicate that, by the use of paraldehyde, we have materially reduced the maternal mortality in eclampsia and have not accomplished this at the expense of the baby.

Smith, Earl Conway: Sodium Perborate Therapy in *Trichomonas Vaginalis* Vaginitis, New Orleans M. & S. J. 94: 37, 1941.

A safe, simple, economical, and prompt method seems to have solved the problem of therapy in *Trichomonas vaginalis* vaginitis, according to Smith. The patient is instructed to douche with a weak lactic acid solution which is followed by the insertion of 10 gr. of sodium perborate in a veterinary capsule daily for fifteen days. Thereafter for seventy-five days the patient continues daily douches of either lactic acid or sodium perborate, depending upon the pH of the vaginal secretions. The patient is discharged as cured when smears show the absence of the organism after three consecutive menstrual periods.

EUGENE S. AUER.

INTRAVENOUS ADMINISTRATION OF BASERGEN DURING THE THIRD STAGE OF LABOR

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A NUMBER of recent reports contend that the ergot alkaloid ergonovine, when administered intravenously immediately after the birth of the baby, not only shortens the third stage of labor but materially reduces the loss of blood. We have studied the action of this drug in this respect in a series of 400 patients and wish to report briefly our findings.

PROCEDURE

The preparation used by us was Basergen,* a water-soluble tartrate of ergonovine, $C_{15}H_{23}O_2N_3$.

As quickly as possible after delivery of the baby 1 c.c. (0.2 mg.) of the drug was given intravenously, usually by the anesthetist. Although the lapse of time between the completion of the second stage and the administration of the basergen varies, the interval rarely exceeded one to two minutes. Within one minute after the injection, expression of the placenta was attempted. An occasional delay of one or two minutes occurred whenever there was no assistant available to tie the cord. While it was necessary in most instances to express the placenta by compressing the anterior and posterior surfaces of the uterus, spontaneous expulsion within two minutes after the administration of basergen was by no means uncommon.

In a control series of 200 patients no attempt was made to expedite the separation of the placenta. In this group, the placenta, after spontaneous separation, was expressed by pressure on the fundus, and the patient was then given an injection of 1 c.c. each of ergone and posterior pituitary extract. The time of placental expulsion as well as the loss of blood were recorded for comparison.

Both groups comprised a consecutive number of patients regardless of the method of delivery, cesarean sections being excluded.

DURATION OF THE THIRD STAGE

As recorded in Fig. 1, a definite shortening of the third stage of labor occurs in an appreciable number of patients when basergen is given. A third stage longer than ten minutes occurred in only 12 per cent of the basergen group, as compared to 36 per cent of the controls. In other words, 88 per cent of the basergen patients against 64 per cent of the controls experienced a third stage of ten minutes or less. A third stage of five minutes or less occurred in 59 per cent of the basergen patients as against 25 per cent of the controls.

*A product of the Sandoz Chemical Works, Inc., New York.

BLOOD LOSS

The blood loss during the third stage was estimated, not measured. However, since this procedure was used in both series the inaccuracy is less objectionable and permits comparison. According to our observations, there was no apparent difference in the loss of blood in the two groups, which is contrary to several recently published reports. We encountered no systemic reactions from basergen.

Tritsch and Behn¹ report in their series that "80 per cent had definitely less than average bleeding after the delivery of the infant and placenta," although 3 cases (2.6 per cent) of profuse bleeding were recorded. Adair and his associates,² in a series of 51 patients, found an average blood loss of 100 c.c., the maximum loss being 300 c.c. in 86 per cent of cases, while 13.7 per cent experienced a loss of 500 c.c. or over, but there were no control cases in their series.

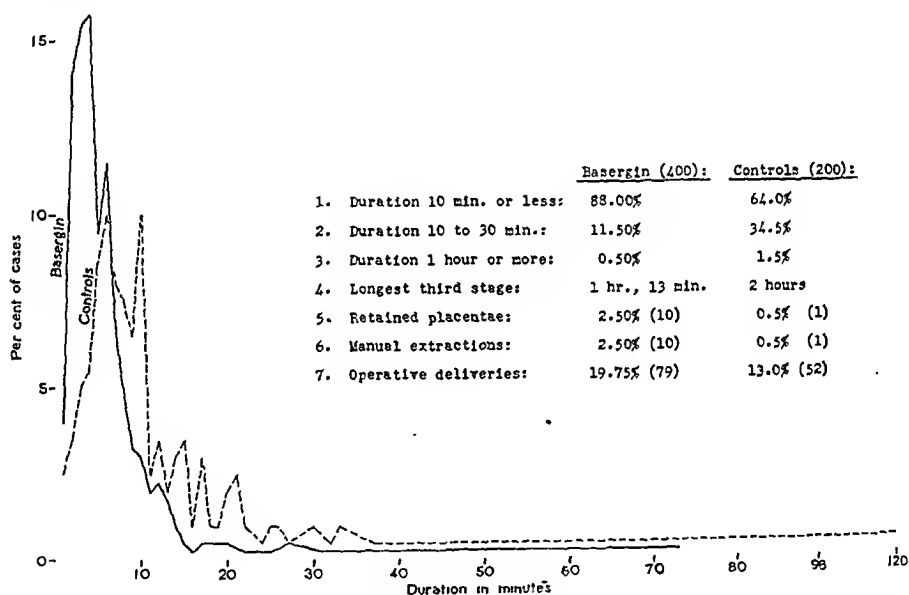


Fig. 1.—Duration of third stage.

Reich³ reports a series of 154 cases in which ergonovine was administered intravenously during the second stage of labor. Of these, 55.8 per cent lost less than 100 c.c. of blood, as against 28.8 per cent of the controls. No hemorrhages over 900 c.c. occurred in those receiving ergonovine, as compared with 9 cases in the control group. In another group of 588 cases in which ergonovine was given after the third stage, Reich noted a loss of 500 c.c. or over in 7.1 per cent as against 16.1 per cent in 548 control cases, where ergotamine tartrate was given.

In our series, a loss of 300 c.c. or less of blood was noted in 92 per cent of the basergen group as compared with 93.5 per cent of the controls; 300 to 500 c.c. were noted in 7 per cent of the patients given basergen and in 6 per cent of the control series. And finally, a severe hemorrhage of over 500 c.c. occurred in 1 per cent of the basergen patients and in 0.5 per cent of the controls (Fig. 2).

RETAINED PLACENTAS

Retention or incarceration of the placenta, due to uterine tetany, may occur after the use of any ergot derivative. This is the one serious

objection raised to the routine use of these drugs. In our experience manual removal of the placenta was necessary in 10 out of 400 patients, an incidence of 2.5 per cent. In the control group this occurred only once in a series of 200 patients (0.5 per cent). Nine of the placental retentions were due to tetanic contraction of the lower uterine structures. Only in one instance was it due to uteroplacental fusion. However, no difficulties were encountered in the extraction of the placentas from the lower uterine segment. If, when basergen is given, the operator places his or her hand over the fundus and exerts moderate pressure on the fundus as soon as contractions are noticed retention of the placenta is less likely to occur.

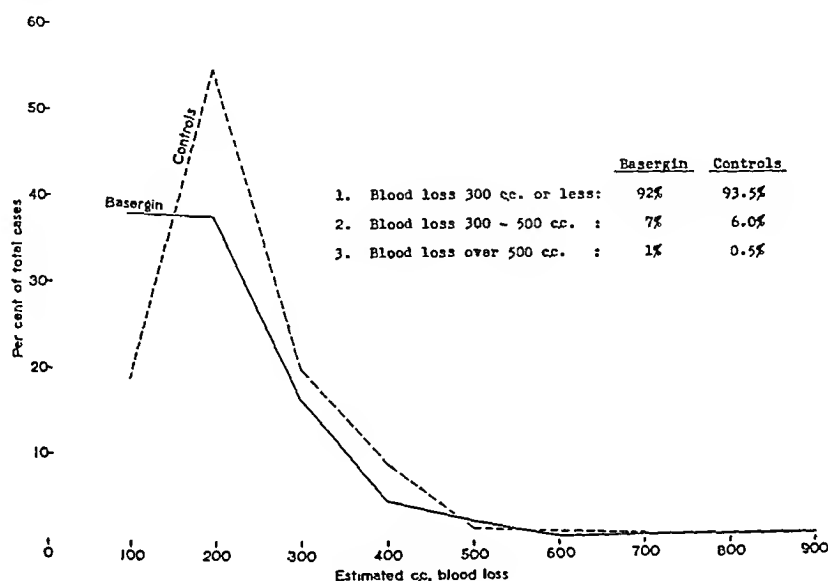


Fig. 2.—Blood loss in third stage.

All but three of the cases requiring manual removal of the placenta presented some abnormality, as indicated in Table I. It is noteworthy that the blood loss in 8 of the 10 cases was less than 300 c.c., in one it amounted to 350 c.c., and one may be considered as an instance of post-partum hemorrhage, since it was 500 c.c. None of the patients in this group developed post-partum fever.

TABLE I

CASES OF MANUAL REMOVAL OF PLACENTA	PLACENTA RETAINED MIN.	BLOOD LOSS C.C.
Basergin Series:		
Case 1: Twins	25	200
Case 2: Premature	5	100
Case 3: Breech	15	100
Case 4: Premature, L.A.D.A.	28	500
Case 5: R.O.P., Manual rotation	36	100
Case 6: Uneventful	4	200
Case 7: Uneventful	73	100
Case 8: Uneventful	42	200
Case 9: R.O.A., low forceps	3.5	350
Case 10: Adherent placenta	31	100
Control Series:		
Case 1: Persistent occiput posterior	98	350

Reich, using ergonovine intravenously during the second stage of labor found, in a series of 154 cases, retained placenta in four instances (3.85 per cent) which necessitated manual removal. Tritsch and Behm similarly report an incidence of 3.47 per cent of retained placenta in a series of 115 cases.

CONCLUSIONS

1. The intravenous use of basergen at the end of the second stage of labor shortens the duration of the third stage.

2. With the exception of about 1.5 per cent of the patients treated, this procedure does not bring about any appreciable decrease in the volume of blood loss in the third stage.

3. Contraction of the lower uterine segment necessitating manual extraction of the placenta is definitely increased after intravenous basergen administered at the end of the second stage.

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THE TREATMENT OF STERILITY WITH "SMALL DOSE" X-RAY THERAPY

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THE treatment of functional menstrual disorders and sterility by irradiation of the ovaries and pituitary gland with small doses of roentgen rays (so-called x-ray stimulation) has been described by many. In 1939, Kaplan,¹ and Mazer and Baer² analyzed fifty-two articles on the subject and described their own extensive experiences. From these reports, they concluded that small-dose irradiation appears to be of distinct therapeutic value in the treatment of irregular menses, amenorrhea, and sterility.

In the face of this evidence, it is surprising to find that this type of therapy is not attempted with greater frequency. Some of the reasons for this are: the belief that x-rays are not effectual in restoring an endocrine imbalance; that many of the reported successes are chiefly coincidental; and the fear of damage to the offspring.³⁻⁹

The following case of sterility is therefore presented again¹⁰ and brought up to date because of the comprehensive clinical and laboratory

evidence of the nature of the endocrine imbalance, and because of the apparently repeated successful responses following small dose x-ray therapy.

REPORT OF A CASE

Mrs. E. P., white, aged 26 years, first sought medical attention on May 21, 1935, because of menstrual irregularities of thirteen years' duration and sterility of six years' duration. Her menses began at the age of thirteen, were generally scant, and averaged six to eight periods a year. Since her marriage, six years prior, there were four episodes of amenorrhea lasting six to seven months each. Occasionally there had been a hemorrhage lasting about one week, and, for the past eight weeks, there had been continuous staining (see Fig. 1). Previous treatment for her sterility had been unsuccessful.

Physical examination revealed an obese patient weighing 215 pounds with a fat distribution suggestive of pituitary deficiency (girdle obesity, apronlike abdomen, narrow ankles and wrists, scant pubic and axillary hair). Examination of the pelvic organs revealed a slightly enlarged right ovary. Rubin and Hühner tests were normal. The husband's spermatic fluid was found to be normal. Roentgenographic examination of the skull revealed a normal sella turcica.

The patient was given the following hormone therapy in 1935 without benefit: oral medication with anterior pituitary extract (5 gr. emplets); thyroid extract (0.25 gr.) 3 times daily for one month; intramuscular injections of A.P.L. (anterior pituitary-like hormone) (2 c.c. each) twice weekly for one month; three courses of injections of prephysin given in December, 1935, January, and February, 1936, each course consisting of 1 c.c. daily for ten days; the last course was followed by 3 injections of progynon-B (2,000 R. U. each) in one week; and in March, 1936, the patient received 3 bi-weekly injections of A.P.L. (2 c.c. each). In spite of this treatment, the menses remained irregular (see Fig. 1).

A comprehensive endocrine study was conducted. Four endometrial biopsies were taken on March 30, April 6, May 29, and June 4, 1936. The first one, taken on March 30, showed only moderate luteinization, but, the one taken the following week, instead of showing more advanced luteinization, showed a proliferative phase. The third biopsy was deferred for three weeks in order to study the same phase in a succeeding menstrual period. It was taken on May 29, and showed very slight luteinization. Once again the following biopsy showed only a proliferative endometrium. Thus the endocrine imbalance consisted in part of an incomplete or abortive luteinization process. At four consecutive intervals of about one week (May 12, 19, 28, and June 4, 1936), bio-assays of twenty-four-hour specimens of urine, taken during the middle of a two-month period of amenorrhea, failed to reveal any prolactin or estrin, except for 13 rat units of estrin in the last specimen (see Fig. 1). Two of the aforementioned endometrial biopsies were taken on the same day as the last two bio-assays. It was decided to administer small dose x-ray therapy.

Four x-ray treatments were given from June 25 to July 5, 1936, delivering in four treatments a total dose of 80 roentgens (measured with back scattering) to the pituitary gland and 80 roentgens to each ovary. One month later, the patient began to menstruate regularly once a

month for the first time in her life. After the third regular menstrual period, it was decided to determine whether the restored monthly bleeding was accompanied by normal cyclical endometrial changes. Consequently, on the day preceding the fourth expected period (Oct. 29, 1935), a premenstrual endometrial biopsy was taken.

In the microscopic examination of this endometrium, Dr. William Antopol found "endometrium in lutein phase with an early embryo." A detailed study of this embryo by Scipiadès¹¹ at the department of

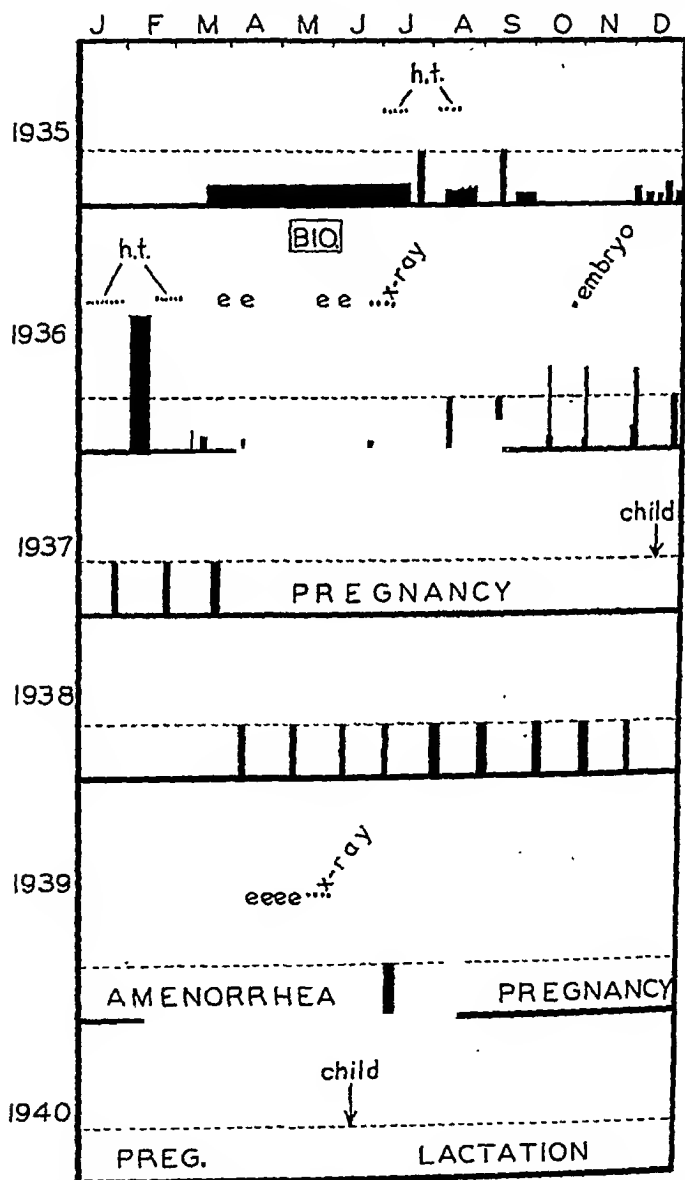


Fig. 1.—Monthly menstrual chart, illustrating clinical course over a period of six years. The solid blocks represent menstrual flow; the broken line represents the normal level of menstrual flow. 1935: Menometrorrhagia alternating with amenorrhea; *H.T.*, hormone therapy. 1936: *H.T.*, hormone therapy, associated with a severe hemorrhage; *E*, endometrial biopsies which showed incomplete luteinization; *Bio.*, bio-assays of prolactin and estrin in the urine (see text); *X-ray*, small dose x-ray therapy; *Embryo*, accidentally removed by suction curettage (see text). 1937: Normal child born in December. 1938: Regular normal menses. 1939: Amenorrhea characterized by absence of lutein effect as shown by four weekly endometrial biopsies (*E*); *X-ray*, small dose x-ray therapy. 1940: Normal child born in June.

embryology, Carnegie Institution of Washington, revealed "that, among the young human embryos already recorded in the literature, this specimen falls between the Kleinhans and the V. Mollendorf 'Sch.' Thus it occupies the third or at the most the fourth place, with its degree of trophoblastic differentiation and its estimated age of 11 to 12 days." Thus three months after x-ray therapy, the patient became pregnant for the first time in her life.

In spite of this accidental abortion the patient continued to menstruate regularly. No further treatment was given. Finally, in April, 1937, nine months after the small dose x-ray therapy, she became pregnant again. During the first two months of this pregnancy, the patient had pelvic discomfort and occasional spotting. She was given injections of progestin (Proluton) and calcium and wheat germ oil for one month, because of threatened abortion, due possibly to lutein deficiency. She was finally delivered at full term of a normal female child in December, 1937.

The patient nursed the baby for five months, although supplementary feedings were given. Menstrual bleeding returned four months after delivery. It was normal and regular except for a missed period in July, 1938.

Following her menstrual period in October, 1938, there was a period of amenorrhea of eight months' duration. During this time two Friedman tests were negative for pregnancy. Another series of four consecutive weekly endometrial suction biopsies were taken on April 20 and 27, May 4 and 11, 1939. All of these showed the endometrium to be in proliferative phase. There was no evidence of any lutein activity. Thus the ovarian failure had returned in a more severe form and was now characterized by amenorrhea and absent luteinization.

Two days after the last endometrial biopsy, a second course of small dose x-ray therapy was given. From May 13, 1939, to May 19, 1939, a total dose of 80 r. (measured with scattering) was delivered in four treatments to each ovary and to the pituitary gland. There was no menstrual period in June, but there were normal periods commencing July 3, and Aug. 9, 1939. She then became pregnant. There was no menstrual period in September. There were two positive Friedman tests on October 5 and 10, 1939. On Oct. 24, 1939, the patient developed pelvic cramps and spotting. A diagnosis was made of threatened abortion, which could be interpreted as another manifestation of deficient progestin activity. She was therefore given fourteen injections of 5 mg. of proluton each, three times a week. After the second injection, the pelvic pains and spotting disappeared. Thereafter, although symptom-free, she was given 2 mg. of proluton twice weekly for four months. The pregnancy proceeded uneventfully and on June 8, 1940, the patient was delivered of a normal male child. She nursed this child for nine months. There was no menstrual period during this time, and for six months thereafter, up to September, 1941.

DISCUSSION

This case strongly suggests that small dose x-ray therapy can favorably affect sterility due to ovarian deficiency. In 1935, the patient's sterility was accompanied by irregular menses, possible estrogen deficiency (as evidenced by bio-assays), and faulty luteinization (as evi-

denced by endometrial biopsies). The first course of small dose x-ray therapy was followed by normal menses and two pregnancies within nine months. The first pregnancy was accidentally interrupted by a premenstrual endometrial biopsy which removed a twelve to fourteen day old embryo, which proved to be the third or at most the fourth earliest embryo in the history of medicine. The monthly cyclical bleeding was not thereby disturbed. The second pregnancy resulted in the delivery of a normal child at full term. In 1939, four years later, the clinical picture of ovarian deficiency returned in a more severe form, as evidenced by amenorrhea and absent luteinization. A second course of small dose x-ray therapy was followed by restoration of normal menses and a third pregnancy with delivery of a normal child.

This case further illustrates the fact that the successful response to therapy of an endocrine imbalance, when viewed over a period of many years may be only temporary. The organism, after responding favorably for a time, may revert to the original deficiency picture. In the above case this was not unexpected, because the endocrine deficiency was profound, as indicated by irregular menses ever since puberty, hypopituitary type of obesity, six-year duration of sterility, and faulty luteinization.

The possibility that the favorable result might have been coincidental is to a great extent eliminated because of the prompt response to each course of x-ray therapy.

The original designation of this type of therapy as "x-ray stimulation" has been discarded in favor of the noncommittal "small dose x-ray therapy." It has not yet been established that small doses of x-rays will actually stimulate the ovaries. It is possible that this type of therapy can destroy some inhibitory factor.

Martius and Kroning¹² have shown that small amounts of roentgen irradiation (5 to 50 r. at the surface) can so damage the follicle apparatus of rats and mice as to produce appreciable variations from normal of the estrus cycle. Evidence of the possible existence of an inhibitory factor in the ovary, which could be neutralized by the irradiation is seen in the work of Stein and Cohen,¹³ and Robinson,¹⁴ who have successfully treated amenorrhea and sterility by removal of the cystic portions of both ovaries; and by one of us (M. F.) who has successfully treated several cases of dysmenorrhea and painful breast hyperplasia by unilateral roentgen irradiation of one cystic ovary with inhibitory doses of roentgen rays.

The evidence concerning possible damage to the unfertilized ovum with resultant injury to the offspring has been based chiefly on the effect of x-rays on the fruit fly (*Drosophila melanogaster*),^{3-7, 15} and to a lesser extent the mouse and guinea pig.⁸ The frequency with which difficulties are encountered in attempting to transpose the results of animal experiments to human beings is well known. This species difference to

which many biologic phenomena are subject is also observed in the field of radiation genetics. Even should the human germ cells eventually be shown to be capable of producing mutation forms as a result of sub-lethal radiation damage, the statistical probability of a previously irradiated ovum ever resulting in a monstrosity, following fertilization, is so small as not to constitute a hazard.

The majority of sterile women who respond successfully to small-dose irradiation usually menstruate for a varying number of months before conceiving. Thus, the ovum which eventually becomes fertilized may very likely have been quiescent and inactive within a primordial follicle during the actual exposure to radiation, and in this state, it would be relatively radioresistant at that particular time.

Therefore, in view of the fact that the inevitability of germ plasm damage to the *human* ovum from small-dose irradiation has not yet been demonstrated, one ought not at this time deny this effective type of treatment to a woman who ardently desires a child. The possible theoretical dangers should be explained to the patient and the final decision left to her.

CONCLUSIONS

1. Roentgen rays administered to the ovaries and pituitary gland in small doses are capable of correcting an ovarian dysfunction of a deficiency type accompanied by sterility.

2. A case is reported wherein two separate episodes of ovarian deficiency with sterility in the same patient were each successfully treated with roentgen rays.

3. Though a review of the experimental evidence based on lower animals suggests the possibility of harmful effects to the germ cells of small doses of radiation, there is as yet no evidence and small likelihood that small-dose x-ray therapy constitutes a real hazard to the human ovum.

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AN ANALYSIS OF LATE MORBIDITY IN ONE HUNDRED CASES OF PREGNANCY TOXEMIA

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REPORTS in the literature show that considerable vascular and/or renal morbidity may be found in toxemia patients at the time of follow-up examinations. Toxemia recurs in approximately 70 per cent of the cases. Early investigators attributed the late morbidity to nephritis, whereas contemporary investigators consider the morbidity the result of essential hypertension. The latter interpretation is substantiated by autopsy records^{12, 26, 27} upon patients who have died from hypertension at long intervals, following toxemia of pregnancy. Renal function tests, urinalyses, and urine sediment examinations, at the time of late checkup studies, show that the incidence of significant renal damage is slight in comparison to the incidence of hypertension.

While obstetricians generally agree on the high percentage of late morbidity found in toxemia patients, there is no unity of opinion concerning the importance of the toxemic pregnancy in causing this late morbidity. Some believe toxemia does not injure a normal vascular and renal system, but most obstetricians apparently feel contrariwise. No definite proof for either assumption may be found in the analysis of our patients, but certain details seem worth mentioning which seem to favor the former assumption.

The method by which pregnancy toxemia may cause persistent hypertension has not been satisfactorily demonstrated. That the hypertension may be secondary to renal ischemia produced by vascular damage from toxemia is a plausible hypothesis; however, convincing proof of such vascular damage in these patients has not been given. A kidney lesion, specifically due to toxemia of pregnancy and also capable of producing hypertension, has not been recognized by pathologists. It is confusing to observe that thickening of the basement membrane of the glomerular capillaries, found by Bell³⁸ and others²⁶ in the kidneys of patients who have died from toxemia of pregnancy, is also to be noted in the kidneys of patients who have died from essential hypertension. One might speculate that there is more in common between toxemia of pregnancy and essential hypertension than is commonly believed. The significance of basement membrane thickening in glomerular capillaries to the cause of essential hypertension and toxemia of pregnancy is not clear since the

same lesion is found in the kidneys of patients who died of other causes²⁶ without a history of either of these hypertensive syndromes.

If the insult of a pregnancy toxemia to a normal vascular system can produce essential hypertension, it should be reflected in the hypertension in women as compared with men. Bell,³⁸ in a study of autopsies upon 11,826 men and 5,882 women, found that the percentage of men who died from the sequelae of hypertension was greater than that of women. Statements to the contrary appear in the literature, but no reliable statistics accompany them.

Reid and Teel¹⁶ have published an observation which bears out the contention that much of the late vascular morbidity attributed to toxemia of pregnancy is due to unrecognized, antecedent vascular disease. Thus, they found normal blood pressures during the second trimester of pregnancy in a fairly large number of women known to have essential hypertension; such women when first seen by obstetricians during the second trimester of pregnancy would probably be considered normal and consequently when seen after parturition may be considered morbid as the result of the toxemia. Taking cognizance of this pitfall, Teel and Reid³² suggested a classification of the late pregnancy toxemias whereby a reliable blood pressure recording and urine examination prior to, or in the first trimester of pregnancy, was necessary in order to distinguish pre-eclampsia from essential hypertension and nephritis. If these data were lacking, the case was considered unclassified. Using this precaution, they found that only 21 per cent of 235 patients with mild pre-eclampsia, and one of 49 patients with severe pre-eclampsia had hypertension at a late checkup examination following parturition. This is a much lower incidence of vascular morbidity than is usually reported. It is possible, that with a more complete evaluation of patients' vascular and renal systems prior to pregnancy, the morbidity which can be attributed to toxemia may be reduced even more. It would seem that any statement regarding late vascular and/or renal morbidity, following toxemia of pregnancy which does not include blood pressure recordings and urine findings before pregnancy or in the first trimester, should be considered pure speculation.

Dieckmann and Brown¹⁷ observed a fall in blood pressure during pregnancy in a small number of women with essential hypertension but did not state whether it was limited to the second trimester. We have observed this occurrence, but in our somewhat limited experience, the fall in pressure has been known to occur as early as the first trimester.

Teel and Reid³² attributed the fall in pressure which they observed during the second trimester of pregnancy in women with essential hypertension to a similar but unexplained phenomenon they had observed in pregnant women known to have normal blood pressures. Andross has carefully charted the blood pressure curves of 154 normal women who were observed in our ante-partum clinic from the early part

of the first trimester to parturition; these patients had all been seen prior to pregnancy in the University Hospital and normal blood pressure recordings were found at that time. Andross was unable to detect an appreciable fall in blood pressure in any substantial number of these patients in any one trimester.

CLASSIFICATION OF TOXEMIAS IN 100 PATIENTS WHO RETURNED FOR A LATE EXAMINATION

The toxemias studied by us were classified, as suggested by Teel and Reid, according to what was known of the patients' cardiovascular and renal systems prior to pregnancy or in the first trimester.

TABLE I

CLASSIFICATION	TOTAL NO. CASES	SEVERITY		
		MILD	MOD.	SEV.
Essential hypertension	9	1	4	4
Nephritis	2	1		1
Pre-Eclampsia	12	8	1	3
Unclassified nonconvulsive	71	21	23	27
Unclassified eclampsia	6	0	0	0
Total	100	31	28	35

The patients with essential hypertension were seen in the University Hospital during the first trimester or prior to pregnancy and at one or both times had blood pressure elevations (140/90 or higher), essentially normal urines, and negative histories for nephritis. The patients with nephritis were treated in our hospital for severe acute nephritis several years before their toxemias, and they had returned for checkup examinations prior to pregnancy and were cured so far as could be determined. The patients with pre-eclampsia were seen in our hospital during the first trimester or less than a year prior to pregnancy, and at one or both times had normal blood pressures, essentially normal urines, and negative histories for nephritis. The unclassified nonconvulsive toxemia patients were not seen in our hospital prior to pregnancy or in the first trimester. Hearsay data accompanying these patients to the hospital were lacking in details and verification; they were not sufficiently reliable to permit classification in this report. It is interesting that 52 of the 71 patients in this group had toxemia when they were first seen by us in the second or third trimester. Five of the 6 patients in the eclamptic group developed convulsions before being seen in our hospital. The other eclamptic patient had a mild toxemia when first seen by us in the last trimester of pregnancy; the convulsions developed post partum.

For the purpose of brevity, the details of the criteria used in grading the severity of our cases will not be discussed. It is sufficient to note that the majority of patients included in the severe grade had blood pressures of 160/110 or greater and large amounts of albumin in the

urine (3-plus to 4-plus); the majority of the patients in the moderate group had blood pressures of 160/110 or higher and little or no albumin in the urine; the patients in the mild group had blood pressures of less than 160/110 and slight degrees of albuminuria (less than 3-plus). The presence of marked symptoms, as headaches, etc., or the presence of considerable edema, or significant eye ground changes, accounted for the placing of some patients in a more advanced group than would be indicated by the blood pressure and albuminuria.

Treatment.—All patients were treated conservatively upon a salt free, neutral ash diet and fluids forced.* Patients with mild cases were sometimes permitted to go home but were asked to return for weekly or bi-weekly visits. Patients with moderate and severe cases were hospitalized until the termination of pregnancy. Interruption of pregnancy when necessary was carried out by the method thought to be best suited to the condition of the patient.

TABLE II. TIME INTERVAL BETWEEN PARTURITION OF TOXEMIC PREGNANCY AND THE CHECKUP EXAMINATION

TIME INTERVAL	1-2 YR.	2-5 YR.	5-10 YR.	10 PLUS YR.
No. Patients	38	35	21	6

TABLE III. INCIDENCE OF BLOOD PRESSURE ELEVATIONS, ENLARGED HEARTS, AND PERIPHERAL VASCULAR SCLEROSIS AT THE TIME OF LATE EXAMINATION

CLASSIFICATION OF TOXEMIA	BLOOD PRESSURE ELEVATION AT CHECKUP*			ENLARGED HEARTS	PERIPHERAL VASCULAR SCLEROSIS
	MILD EL.	MOD. EL.	SEV. EL.		
Essential hypertension	4	1	2	1	1
Nephritis	0	0	1	0	0
Pre-eclampsia	0	0	0	0	1
Unclassified nonconvulsive	7	7	12	8	13
Unclassified eclampsia	1	0	0	0	1
Total	12	8	15	9	16

*Mild blood pressure elevation 140-158/90-100

Moderate blood pressure elevation 160-180/100-110

Severe blood pressure elevation over 180/110

Thirty-five per cent of the 100 patients who returned had hypertension; 16 per cent had peripheral vascular sclerosis, and 9 per cent had cardiac enlargement. The peripheral vascular sclerosis was minimal except in 5 patients, all of whom had severe hypertension. All but 3 patients with minimal arteriosclerosis had some degree of hypertension which appeared to be the basis of this morbidity. All cardiac enlargements were the result of hypertension except for one case of rheumatic heart disease.

The Lashmet-Newburg thirty-six-hour renal concentration test was started by the patients at their homes and completed at the hospital

*See R. R. de Alvarez, reference 39.

TABLE IV. ANALYSIS OF KIDNEY FUNCTION TESTS, URINALYSES, AND URINE SEDIMENT EXAMINATIONS AT THE LATE CHECKUP

CLASSIFICATION OF TOXEMIA	KIDNEY FUNCTION TESTS				URINALYSES		URINE SEDIMENTS		
	NO. TESTS	NOR- MAL	MIN. IMP.	MOD. IMP.	ALB.	SUGAR	W.B.C.	R.B.C.	CASTS
Essential hypertension	8	6	2	0	0	1	1	0	1
Nephritis	2	1	1	0	1	0	1	0	1
Pre-eclampsia	12	11	0	1	1	0	0	1	1
Unclassified nonconvulsive	64	51	12	1	6	1	0	4	4
Unclassified eclampsia	6	6	0	0	0	0	1	1	0
Total	92	75	15	2	8	2	3	6	7

where the last two specimens were obtained for analysis, sediment examination, and measurement of specific gravity. A specific gravity of 1.029 to 1.022 was considered indicative of minimal impairment and 1.022 to 1.016 moderate impairment. The heat and acetic acid test was used to detect albumin.

Due to the uncontrolled conditions of the concentration tests, those showing decreased concentrating ability cannot be accepted as positive evidence of renal impairment. Fortunately the patients cooperated eagerly, and we are able to show that 90 of the 92 patients whose tests could be used had normal, or no more than minimally impaired, concentrating ability. Ten of the 15 tests showing minimal impairment disclosed specific gravities of 1.027 to 1.028.

Albumin and casts were found in the urines of three patients. One of these patients gave a history of earlier nephritis; the other two had severe hypertension, no history of nephritis, and their urine findings were considered significant of renal involvement secondary to hypertension. In 9 patients, the urine had either an occasional granular cast or a faint trace of albumin, a finding of questionable significance in view of a normal concentration test in 8. Hypertension was found in 7 of this group and the possibility of mild secondary renal damage could not be excluded. None of this group had a history of nephritis.

TABLE V. RESULTS OF FUNDUSCOPIC EXAMINATION OF THE EYES AT THE LATE CHECKUP

CLASSIFICATION OF TOXEMIA	FUNDI AT CHECKUP*					
	NO.	NORMAL	G1	G2	G3	G4
Essential hypertension	9	2	6	1	0	0
Nephritis	2	2	0	0	0	0
Pre-eclampsia	12	9	3	0	0	0
Unclassified nonconvulsive	68	47	18	3	0	1
Unclassified eclampsia	6	5	1	0	0	0
Total	97	65	28	4	0	1

*G1, eye grounds showed evidence of vascular sclerosis as manifested by vascular attenuation, increase in reflex stripe, tortuosity, and arteriovenous notching.

G2, eye grounds showed more evidence of hypertensive change, as manifested by localized areas of angiospasm.

G3, eye grounds showed edema.

G4, eye grounds showed hemorrhages and exudate.

A few red blood cells were found in the urines of 7 patients, but in no instance was there an accompanying albuminuria or cylindruria.

Although an occasional white blood cell was found in the urines of many patients, significant numbers were found in only three. These three patients had normal blood pressures, and at the time of their toxemia did not have white cells in their urines. No further investigation was carried out on this group.

The degree of vascular sclerosis in the 28 patients showing at fundiscopic examination G1 changes was minimal; in some instances there was debate among the ophthalmologists as to its presence. Eighteen in this group as well as the 5 patients who showed more advanced changes in their eye grounds had hypertension. It, therefore, appeared that there was a definite relation between the eye ground morbidity and blood pressure.

TABLE VI. THE FUNDISCOPIC CHANGES AT THE LATE EXAMINATION IN COMPARISON WITH THOSE DURING TOXEMIA. (44 PATIENTS) THESE PATIENTS HAD SEVERELY ELEVATED BLOOD PRESSURES AT THE TIME OF THEIR TOXEMIAS

CLASSIFICATION OF FUNDI AT TIME OF TOXEMIA		CLASSIFICATION OF FUNDI AT CHECKUP*				
		NORMAL	G1	G2	G3	G4
Normal	2	2	0	0	0	0
G1	28	22	6	0	0	0
G2	2	2	0	0	0	0
G3	9	4	4	0	0	0
G4	3	1	1	1	0	1
Total	44	31	11	1	0	1

*G1, changes in the eye grounds during toxemia were due to angiospasm of a generalized nature producing a generalized attenuation without variation in caliber.

G2, G3, G4, changes are the same as above (see Table V).

Eleven of the 13 patients with residual eye ground pathology had hypertension. The 31 patients with normal fundi at the checkup examination had normal or minimal elevations of blood pressure. Here again the relation between eye ground morbidity and hypertension was apparent.

SUMMARY

The chief morbidity to be found in toxemia patients at late post-partum examination is hypertensive disease.

The observation, published by Teel and Reid, concerning the fall in blood pressure which they observed during the second trimester in women with essential hypertension, makes it seem likely that much of the morbidity which the literature has attributed to toxemia may be due to antecedent, unrecognized vascular disease.

It is suggested that patients who do not have reliable vascular and renal estimations prior to the toxemic pregnancy be omitted from morbidity studies.

In our study there was no evidence of significant vascular or renal morbidity in patients known to be normal prior to their toxemic pregnancies.

This study was carried out with the cooperation of the following doctors and departments in the University Hospital: Harold Falls, Department of Ophthalmology; Fleming Barbour, Department of Ophthalmology; Ralph Cooper, Department of Medicine; Richard Lyons, Department of Medicine.

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The authors performed a thymectomy upon a 17-year-old girl, under local anesthesia. The three indications given for the surgery were marked ease of fatigue, generalized malaise, and a very dry skin. The removed operative specimen measured 11 cm. and weighed 25 Gm.

One year after the operation the patient is reported as viracious, active, and capable of leading a normal life without unusual fatigue. The skin continues to be dry in type. A previous thymectomy was done by the authors, in 1938, upon a patient with myasthenia.

CLAIR E. FOLSONE.

BIOLOGIC ASSAY OF THE ESTROGENS IN PREGNANCY BLOOD

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THE present study deals with the estrogenic potency of human blood in the various weeks of normal pregnancy. The method used is the one originally described,¹ with the exception that the sodium sulfate blood powder was extracted not only with ether but also with 95 per cent ethanol.

A comparison of ether extracts, alcohol extracts, and combined ether and alcohol extracts on the same bloods was carried out on 20 different pregnancy bloods. An analysis of the tabulations in Table I tends to show that ether is a better solvent than alcohol for the estrogens of blood, and that alcohol and ether combined give a slightly better result than when ether alone is used.

Fifteen different pregnancy bloods were hydrolyzed and titered for comparison by the above method. This was done by adding sodium citrate (to prevent coagulation), distilled water, and concentrated hydrochloric acid to pH 2. The blood was then boiled for fifteen minutes in a reflux condenser, cooled, and made to pH 6 with 40 per cent sodium hydroxide. The water was evaporated from the blood on a water bath and the sludge treated as in the method originally described.¹ We found no increase in the estrogenic potency on hydrolyzing blood by this method over the ether and alcohol extracts of aliquot blood samples run directly into the sodium sulfate (Table II).

Ether alcohol extraction of sodium sulfated blood powder was the method of assay employed on 86 pregnancy bloods, covering the various weeks of pregnancy from the fifth to the fortieth weeks. The stage of pregnancy was calculated by determining the number of days from the last menstrual period, and adding ten days. In most cases we were limited to withdrawing 10 c.c. of blood. This accounts for the fact that only 63 of the bloods proved positive. In a majority of instances in the latter weeks, at which period the concentration is high, two or more castrated mice could be used for determining the smallest amount giving a positive estrous reaction (full cornification). Two hundred and eighty-two assays were carried out.

As can be seen from Fig. 1, the estrogen blood level remains approximately at the highest nonpregnant level until the seventeenth week is reached (from 25 to 35 mouse units per liter). From then on, a steady

TABLE I. COMPARISON OF METHODS OF EXTRACTION ON ASSAY OF BLOOD ESTROGENS

CASE	DURATION OF PREG- NANCY, WEEKS	ETHER EXTRACTION		ALCOHOL EXTRACTION		ETHER-ALCOHOL EXTRACTION	
		C.C. OF BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING	C.C. OF BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING	C.C. OF BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING
4376	36	4	++++	5	++++	2	++++
		3	++++	5	-	2	++++
		3	-	4	-	1	++++
		2	-	4	-	1	++++
		1	-	3	-	1	-
						.75	++++
4357	33	10	++++	10	++++	10	++++
		7.5	++++	7.5	++++	4	++++
		5	++++	5	++++	2	++++
		2.5	-	2.5	-	2	++++
						1	++++
						1	++
4397	27½	4	++++	5	++++	3	++++
		3	++++	5	-	2.5	-
		3	++++	3	-	2	++
		2.5	-			2	-
		2	++++			1	-
		2	(Mouse died)				
4354	17	10	++++	10	++++	10	++++
		5	++++	7.5	-	7.5	++++
		3	-	5	-	5	+++ sl.
				3	-	2.5	-
4368	17	7.5	++++	7.5	-	7.5	++++
		5	++	7.5	-	5	++++
		5	-	5	-	4	-
		6	-			3	-
						2	-
4367	15½	12.5	-	12.5	-	10	-
		10	-	10	-	9	-++++
		7.5	-	7.5	-	7.5	+++++
4422	15½					15	-
						15	-
4402	14½	20	++++	20	++++	20	++++
4390 II	11½					20	++++
4388	11	30	++++	30	-	30	++++
4396	9					20	-
						10	-
4360	8½	30	-	30	-	30	+++
4390	7½					20	-
4353	7½	20	-	20	-	20	-
		10	-	10	-	10	-
4379	7	40	-	40	-		
4365	6½	40	-	40	-		
4378	6	40	-	40	-		
4391	6					20	-
4350	5	20	-	20	-	20	(Mouse died)
		10	-	10	-	10	-
4357	5	30	-	30	-	30	-

upward trend is noted which reaches its maximum at term (from 600 to 1,300 mouse units per liter).*

In a previous publication,² the excretion of combined and free estrogens in the urine during pregnancy was described. In this, a

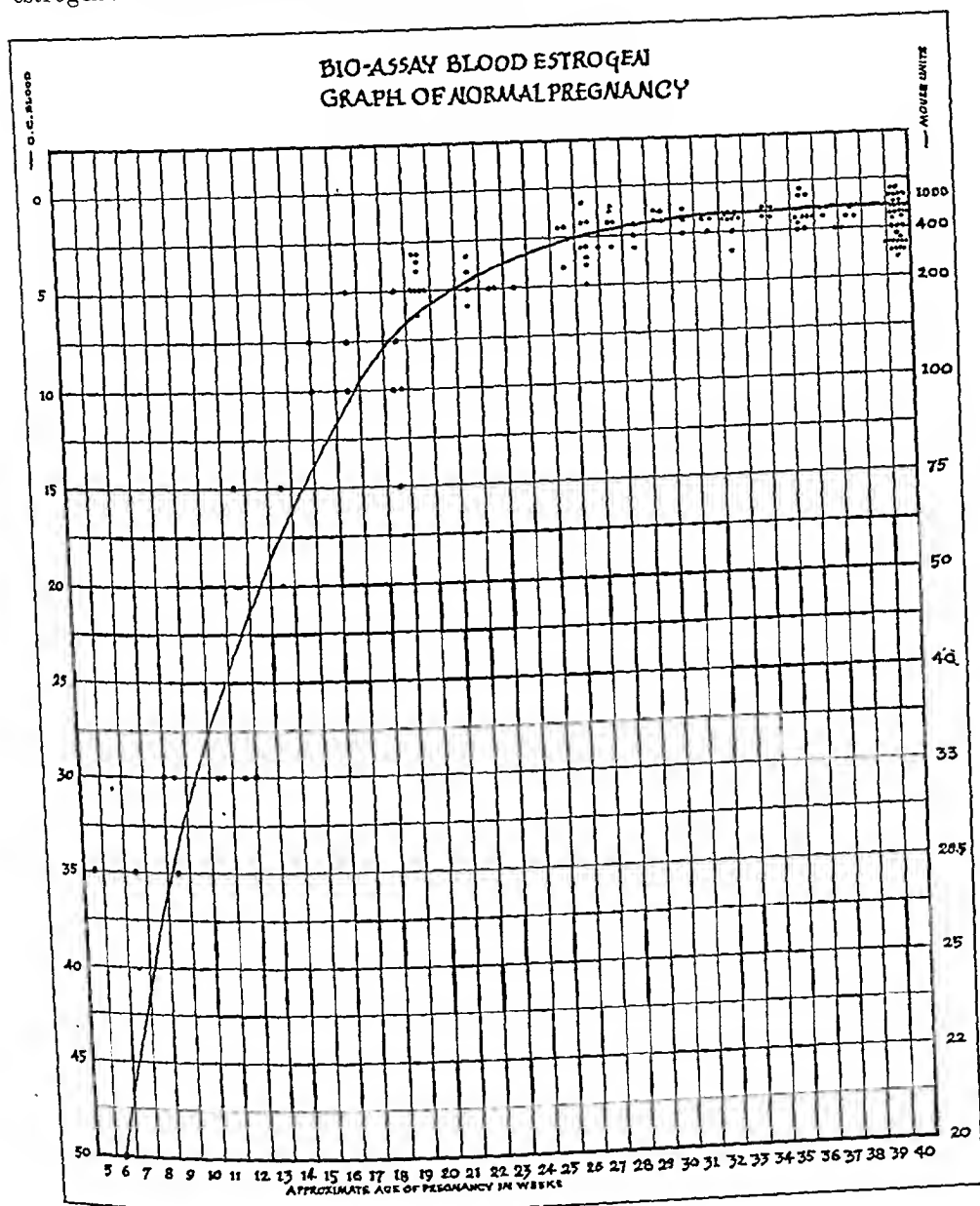


Fig. 1.

marked increase of the excretion of the combined estrogens was noted after the twenty-eighth week, and that of free estrogens after the thirty-second week. In the blood, the estrogens are probably in a free state,

*Under conditions of assay in our laboratory a positive reaction is obtained with 0.08% of estrone in contrast to 0.1% which equals one international unit.

TABLE II. A COMPARISON OF ETHER-ALCOHOL EXTRACTS WITH HYDROLYZED CITRATED BLOOD EXTRACTS

CASE	DURATION OF PREGNANCY, WEEKS	ETHER-ALCOHOL EXTRACTION		SODIUM CITRATE HYD.	
		C.C. BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING	C.C. OF BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING
4602	40	2.2	+++	4	-
		2	++++	3	-
		2	++++	2	-
		1.8	++++	1.5	-
		1.5	-	1	-
		1	++++	1	-
		1	++++		
		1	-		
4603	40	3	++++	4	-
		2.5	++++	3	-
		2	+++	2.5	-
		1.5	++++	2	-
		1.5	-	1.5	-
		1	-	1	-
		1	-	1	-
		1	-		
4607	40	3	++++	2	++++
		2.5	++++	2	++++
		2.2	+++	1.5	++++
		2	-	1.2	+++
		2	-	1.2	-
		1.5	-	1	+++
		1.2	-		
		1	-		
4621	40	3.5	+++	4	-
		3.5	-	3.5	-
		3.2	++++	3.5	-
		3	+++	3.2	-
		5	-	3	-
		2.5	-	2.5	-
4643	40	3.5	++++	4	-
		3.5	++++	4	-
		3.25	+++	3.75	-
		3	+++	3.5	-
		3	++++	3.5	-
		2.5	-	3	-
		2.25	-		
4655	40	3.5	++++	4	-
		3	++++	4	-
		2.5	+++	3.5	-
		2.25	-	3	-
		2.25	-	3	-
		2	-	2.5	-
4626	40	2	+++	4	-
		1	+++	3	-
		1	+++	2	-
		1	-	1.5	-
				1	-
4803	17	10	+++	10	+++
		10	-	10	+++
		8	-	8	-
		7	-	7	-
		5	-	5	-

TABLE II—CONT'D

CASE	DURATION OF PREGNANCY, WEEKS	ETHER-ALCOHOL EXTRACTION		SODIUM CITRATE HYD.	
		C.C. BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING	C.C. OF BLOOD EQUIV. USED	MOUSE VAGINAL SMEAR READING
4724	13	30	++++	35	-
4672	12	20	++++	20	(Mouse died)
		10	-	10	-
4694	12	20	++++	20	-
		15	++++	15	-
4722	10½	35	-	35	-
4649	7	5	-	5	-
		4	-	4	-
		4	-	3.5	-
		3.5	-		
		3.5	-		
4720	7	35	++++	35	-
4769	5	35	++++	35	++++

because, as shown, the yield following hydrolysis was not increased. The small amount of estrogens found in the blood during the early weeks shows some parallelism with the small amount of free estrogens found in the urine at the beginning of pregnancy. In the urine the free fraction of the estrogens increases from 2 to 22 per cent of the total estrogens as the pregnancy advances to term. In the blood it rises from 20 units in the fifth week to 1,333 toward the end of pregnancy.

SUMMARY AND CONCLUSIONS

1. A biologic assay of the estrogens in 86 pregnancy bloods, covering from the fifth to the fortieth weeks, was performed.
2. Attempts to increase the yield by hydrolysis of the blood were unsuccessful.
3. Combined ether and alcohol extraction was found to be more efficacious than ether extraction or alcohol extraction alone.
4. A graphic presentation of the results of this study shows that the greatest amount of estrogens is present just before labor.
5. The estrogens in the blood increase slowly from the fifth week of pregnancy in each individual case; but not before the seventeenth week did any of the cases studied reach a level above the upper limit of estrogens in nonpregnant women.
6. From the seventeenth week of pregnancy progressive increase of estrogens in the blood takes place. Some parallelism of blood estrogen increase and free urinary estrogen increase appears to exist.
7. The estrogens in the blood probably circulate as free estrogens.

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THE LENGTH OF THE MENSTRUAL CYCLE

A STUDY OF 150 NORMAL WOMEN

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SINCE investigations during recent years have emphasized a definite time relationship between ovulation and menstruation, the length of the normal menstrual cycle has become more than a purely academic problem. It has long been taught that normally menstruating women do so at regular intervals. Expression of this view abounds in medical periodicals and even in modern textbooks. The general consensus of opinion is that twenty-eight days constitute the so-called "normal" cycle.

Kennedy (1937)⁷ stated that of 10,000 cycles, 7,339 were twenty-eight days long, while 582 were twenty-one days long, and the rest were scattered over other days of the cycle. Nakagawa (1931)⁸ writes that 97 per cent of a selected group of 2,000 women menstruated "regularly." Sanes (1916),¹¹ Hajek (1933),⁶ and others report similar findings. Novak¹⁰ quotes from the following workers who conclude that a majority of women have twenty-eight-day cycles: Kelly, 94.2 per cent; Kreiger, 70 per cent; Webster, Hart and Barboul, 71 per cent; Sanes, 72 per cent; and Meyer, 69.7 per cent. Novak in Curtis' *Textbook of Gynecology* stated that in most patients menstruation occurred at relatively regular intervals, and that the most common menstrual cycle was twenty-eight days long.

It is, however, self-evident that the ideal group for such studies would comprise women who, in addition to having some interest in or some good reason for keeping calendar records carefully, are at the same time normal from a gynecologic standpoint.

Studies of such individuals have been made in the past few years by Fluhmann,⁴ Gunn,⁵ and Allen.¹ Some of these records were kept by nurses and by college women whose age and manner of living might leave some doubt as to the normality of their menstrual behavior. However, according to the work of Arey² (1939), which our own findings confirm, occupation apparently does not alter the menstrual cycle significantly and may be disregarded in statistical studies. From analysis of 12,452 cycles which were actually recorded by 1,089 women and reported in papers published between 1889 and 1937, Arey also concluded that ordinary hospital records, oral testimony and similar data are unreliable.

The purpose of the present report is to make available information obtained from accurately recorded calendar data collected in the course

of consultations given to a group of 150 married women attending the Rhythm Department of the Fertility and Endocrine Clinic of the Free Hospital for Women. These women were mostly housewives; the majority were mothers in the third and fourth decades of life; they represented a composite of nationalities. No women were accepted for admission to this clinic who were not considered to menstruate normally. Retroversion, chronic cervicitis, and perineal lacerations and relaxations were the only pathologic entities recorded.

Upon admission to the clinic, the patient was given a calendar on which she was instructed to circle the date of the first day of flow each month. The calendar, marked accordingly, was returned to the clinic by the patient either in person or by mail within a few days after the onset of catamenia, in order that the "safe" and "unsafe" periods might be marked by a member of the clinic staff. Since these women realized the importance to themselves of accuracy and promptness in reporting the start of the menses, such a group would appear to constitute an ideal one for the statistical study of cycle lengths, the more so in view of the fact that their gynecologic condition was normal.

TABLE I. DISTRIBUTION OF CYCLE LENGTHS

DAYS	NO. OF CYCLES	DAYS	NO. OF CYCLES
10-14	2	31	175
15-19	10	32	90
20	10	33	61
21	11	34	46
22	35	35	36
23	57	36	15
24	108	37	8
25	204	38	7
26	296	39	5
27	357	40	2
28	369	41-45	6
29	286	46-50	4
30	206	51-100	4

TABLE II. ANALYSIS OF DATA

Nationality	American	Mean cycle length (days)	28.4
Occupation	Housewife	Average deviation of cycles from group mean (days)	1.7
Number in group	150	Standard deviation of cycles from group mean (days)	2.2
Age range (years)	19-42	Occurrence of cycles equalling group mean (%)	15.0
Mean age (years)	30.9	Longer than group mean (%)	38.4
Total number of cycles	2460	Shorter than group mean (%)	44.3
Range in number cycles reported	7-49		
Mean number cycles per person	16.4		
Shortest and longest cycle (days)	10-55		
Modal cycle length (days)	28		

RESULTS

This group of 150 women was observed for a total of 2,460 cycles, the menstrual cycle being defined as the interval between recurrences of periodic physiologic uterine bleeding.

They ranged in age from 19 to 42 years with a mean of 30.9.

Per person, the number of cycles ranged from 7 to 49 with an average of 16.4 cycles.

The shortest and longest cycles were ten and fifty-five days, respectively. Each occurred once (Fig. 1).

The most frequent cycle was twenty-eight days long; this was observed in 369 cases only 15 per cent of the series (Table I).

The mean of all cycles was 28.4 days, and the average deviation from the group mean was 1.7 days. The standard deviation was 2.2 days; giving a standard range of cycle length of 25.2 to 30.6 days; 68.1 per cent of cycles fell within this range.

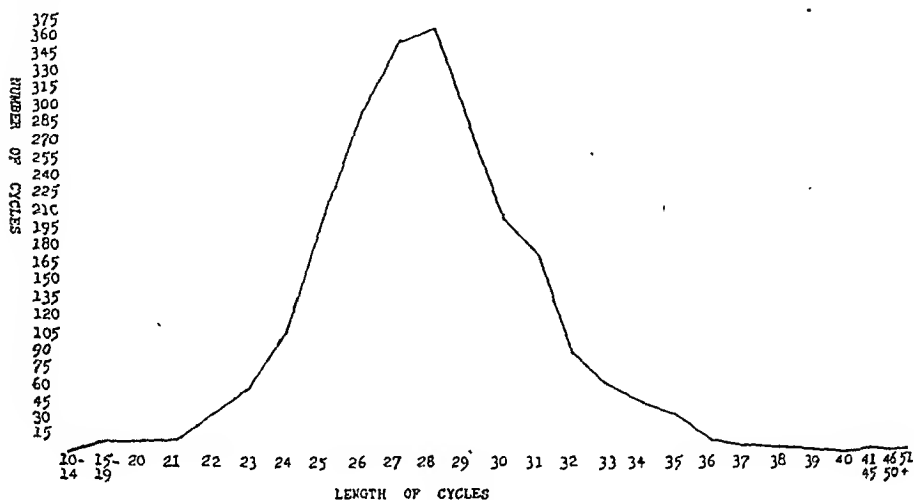


Fig. 1.

Thirty-eight and four-tenths per cent of the cycles were longer and 44.3 per cent were shorter than the group mean of 28.4 days (Table II).

It is noteworthy that of the entire group of 150 women only one showed a deviation of as little as ± 1 from the mean of her cycle lengths. Of 7 cycles recorded by her, 5 cycles were twenty-seven days long; one was twenty-six and one was twenty-eight days. Such a low percentage of relatively regular catamenia clearly substantiates Fraenkel's well-known statement: "Das einzig Regelmässige an der Regel ist ihre Unregelmässigkeit" (the one regularity of the menstrual cycle is its irregularity).

SUMMARY AND CONCLUSIONS

1. An analysis of 2,460 calendar records of 150 normal women was made with the view of adding to the relatively few recorded observations on the human menstrual cycle. The cycle is defined as the interval between recurrences of periodic physiologic uterine bleeding.

2. The most common cycle was 28 days (which occurred in 15 per cent of cycles studied), and the average length of all cycles studied was 28.4 days.

3. There was no instance of absolute regularity in this series. The most regular cycles were in patients who reported the fewest. These would doubtless show more irregularity were a greater number of cycles reported.

4. There is no evidence of groupings in the multiples of 7; i.e., twenty-one, twenty-eight, or thirty-five-day cycles; nor do the cycles seem to fall into a few categories.

5. The distribution of cycle lengths follows the Gaussian curve.

6. This series again refutes the theory of the regularity of the human cycle, thus necessitating caution in judging the applicability and merits of the so-called "safe period" as a means of birth control.

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SPONTANEOUS PAINLESS PARTURITION IN A CASE OF PREGNANCY COMPLICATED BY TRANSVERSE MYELITIS*

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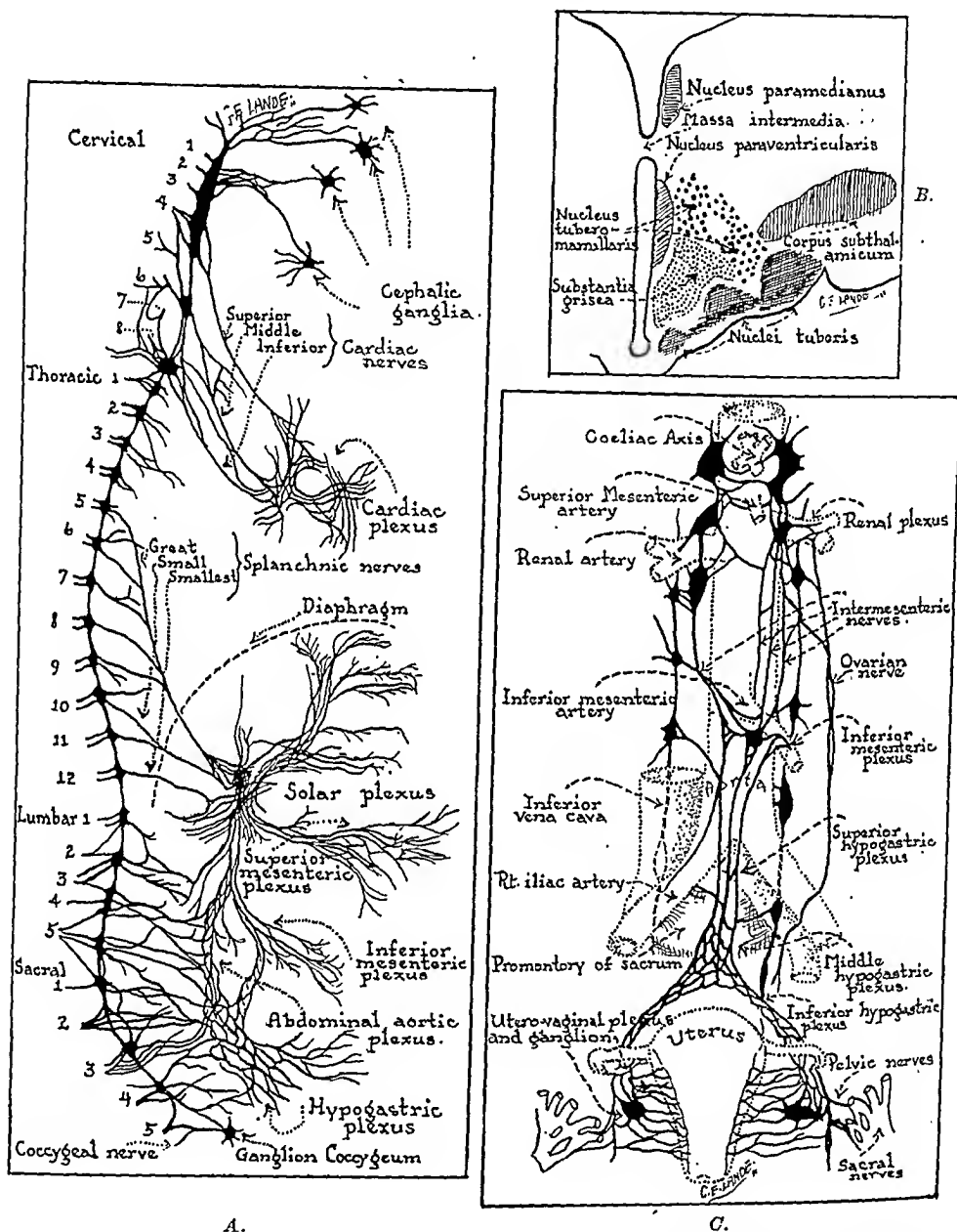
THE nerve control of the uterus has been the subject of study for many centuries. Our present knowledge concerning this nerve control is limited because of its multiple ramifications and because of technical difficulties in tracing its origin.

Roughly the nerve control can be divided into four divisions: (1) centers in the brain; (2) tracts in the spinal cord; (3) extrinsic connections with the spinal cord, and (4) intrinsic nerves in the uterus.

Centers in the Brain.—The centers in the brain are indefinite. It is believed at present that the highest center for uterine nerve control lies in the diencephalon. According to Kuntz,¹ diencephalic nuclei which are known to control autonomic function are located in the hypothalamus

*Presented, by invitation, at a meeting of the Philadelphia Obstetrical Society, November 6, 1941.

and the wall of the third ventricle (Fig. 1, *B*). Which of these nuclei influence uterine muscular contraction is not known. In general, the descending pathways from these diencephalic autonomic centers involve



A.

C.

Fig. 1.—A, Scheme showing general plan of the coarser portions of the sympathetic nervous system and its principal communications with the cerebrospinal system. (After Flower, modified by Morris.) B, Diagrammatic cross-section of the diencephalon showing relative positions of the diencephalic autonomic nuclei. (After Kuntz, modified.) C, Diagrammatic illustration showing the preaortic plexuses and the extrinsic nerve supply of the uterus. (After Dahl, modified.)

mainly the periventricular system to the tectal and dorsal tegmental region and from there, the tectobulbar and tectospinal tracts and dorsal longitudinal fasciculus, respectively.

Spinal Cord.—In the spinal cord, ganglia are located in the intermediolateral column of the dorsal and lumbar regions, from which fibers emerge through the lumbar spinal nerves and join the sympathetic trunk. From there they may go to form the sympathetic plexuses (Fig. 1, A). Their function is excitation of the uterine musculature. Other ganglia are located in the medioventral column in the sacral region, from which fibers go directly to the terminal ganglia through the sacral spinal nerves (Fig. 1, A). The function of the latter is supposed to be inhibition of uterine muscular contraction, but recently this function has been subject to question.

Extrinsic Spinal Cord Connections.—Connections between the spinal cord and the uterus are numerous. Fibers from the lateral branching inferior hypogastric plexus join fibers directly from the lower lumbar sympathetic trunk and the second, third, and fourth sacral nerves to form the uterovaginal plexus. The latter is located chiefly at irregular intervals along the attachment of the uterus and broad ligament (Fig. 1, C).

Intrinsic Uterine Nerves.—From the above-described plexuses, nerve fibers both myelinated and nonmyelinated penetrate all the uterine muscle layers but are not believed to penetrate the endometrium. Reynolds² believes that conduction of nerve impulses to and in the uterus proceeds by a succession of short synoptic pathways.

Normally parturition may be considered as a reflex act, the center of which is situated in the lumbar region of the spinal cord. Uterine function may, however, be independent of central nerve control. Numerous experiments by Reiman,³ Rein, Goltz and Eward, Brachet, Kaminester and Reynolds,⁴ Reynolds, Cannon and Rosenbluth⁵ demonstrate this independence. Bach⁶ believed that sympathectomy might interfere with parturition. Yaskin and Andrussier⁷ quoting Schumann and Fist's case believed that lesions in the sacral region interfered with normal parturition but did not interfere with uterine contraction. Instances of spontaneous labor in cases of decentralized uterus are reported in the literature. The following case, which occurred in the wards of the Philadelphia General Hospital, services of Dr. Howell and of the late Dr. Frank Hammond, adds further evidence of this independence.

CASE REPORT

H. O., a 37-year-old colored female, was admitted to the maternity ward Nov. 14, 1939, complaining of pain in the back, numbness of the legs and inability to walk. She stated that she was well until her last menstrual period which occurred Mar. 8, 1939. In November she developed urinary retention. Physical examination revealed an obese colored female lying in bed in apparent pain and unable to move her extremities. Eye ground examination revealed evidence of vascular sclerosis. Neck showed an enlarged thyroid. Heart was somewhat enlarged and forceful. Chest was normal. Blood pressure was 155/100. Left breast was normal. Right breast revealed two nodules, one in the left lower quadrant which was freely movable and the second in the left upper quadrant which was hard and irregular. Abdomen was enlarged to the size of a pregnancy at or near term.

Neurologic examination: Both pupils were equal but irregular in outline. Response to light and accommodation was prompt on the right, sluggish on the left. Corneal reflexes were normal. No facial or lingual

weaknesses were present. Abdominal reflexes could not be elicited. Complete flaccid paralysis of both lower limbs was present. A partial bilateral foot drop was evident. Patellar and ankle jerks were absent. Pain and thermic sensations were lost below the tenth thoracic nerve level as well as vibratory and position sense.

X-ray showed osteolytic metastases involving the twelfth thoracic and third and fifth lumbar vertebrae. A fetus almost at term was seen in breech presentation.

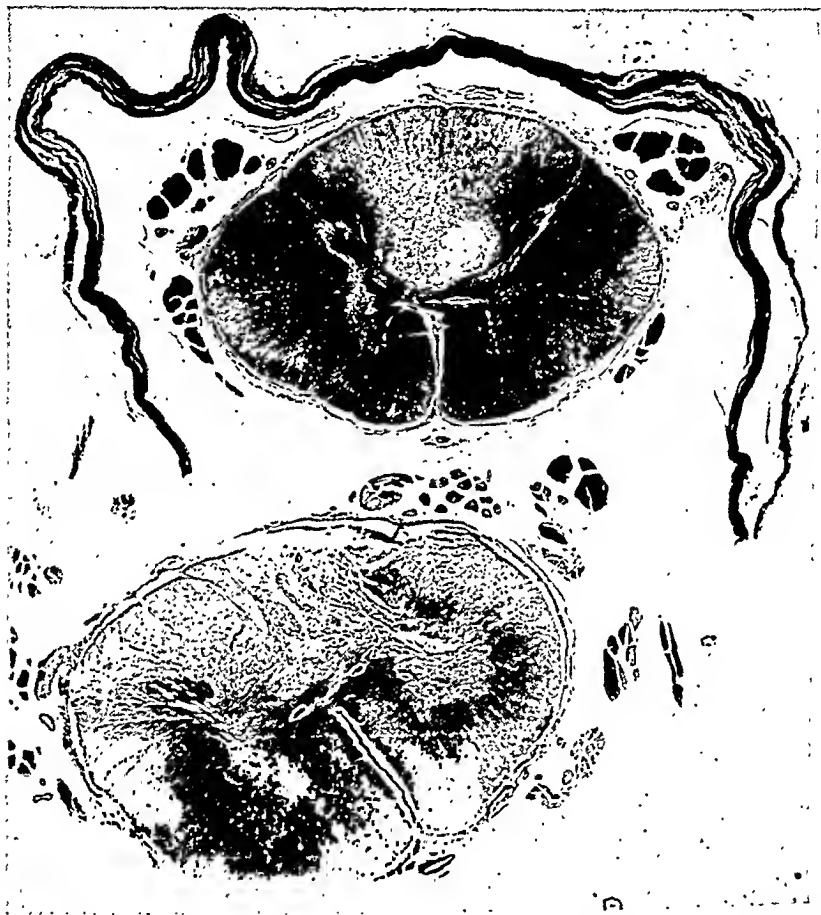


Fig. 2.—Cross section of the spinal cord showing myelomalacia of the lower thoracic segments and ascending secondary degeneration of the upper thoracic segment. Magnification 4X.

Laboratory tests: Urine contained five to ten leucocytes, 2 to 5 epithelial cells and was otherwise normal. Blood counts were normal. Blood Kahn test was negative. Nov. 26, 1939: 10 A.M.: The membranes ruptured spontaneously. Patient had no feeling of labor pain whatsoever. 12 noon: Fetal heart was 132 in upper right quadrant. 12:50 P.M.: A foot appeared through the vulva, then the second foot, followed by the buttock. The arms were decomposed. The shoulders were delivered, followed by the head. The baby breathed spontaneously. The patient was given intravenous ergotrate, gr. 1.320. The uterus contracted well. Very little bleeding was encountered. The baby weighed 6 pounds 8 ounces.

Placenta was delivered intact and weighed 1 pound 3 ounces. Histologic studies of the placenta revealed nothing suggestive of malignant epithelial cells.

The remarkable feature of the delivery was the total absence of pain. The patient was conscious of her experience only through sight. She felt nothing whatsoever.

Aside from some fever, the progress of the case was normal from an obstetric viewpoint. She was transferred to the cancer ward where a simple mastectomy was performed. They found (a) poorly differentiated adenocarcinoma and (b) multiple fibroadenomas. Patient recovered from the operative procedure; however, her general condition was fundamentally bad and she died April 8, 1940, more than four months after delivery.

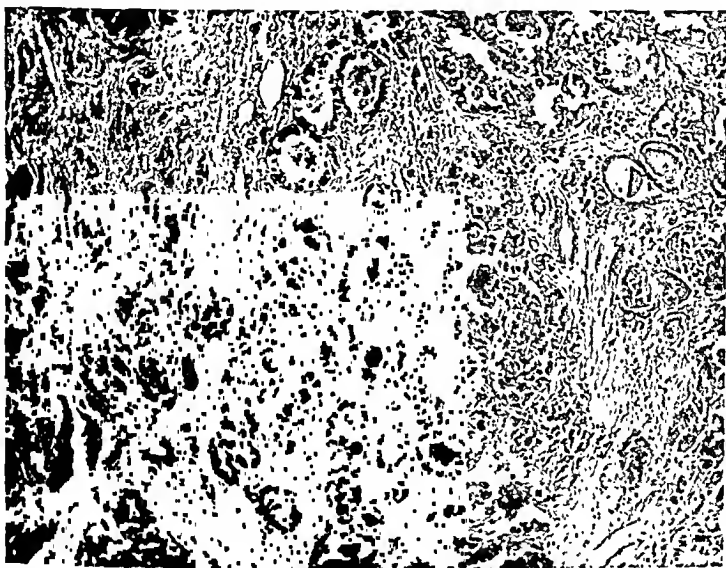


Fig. 3.—Cross section of the epidural tissue of the lower thoracic spinal cord segment showing metastatic adenocarcinoma. Magnification 92X.

Necropsy revealed the following outstanding features: Adenoma of the thyroid with hemorrhagic and cystic degeneration, mild coronary sclerosis and myocardial infarction, embolism in the left pulmonary artery, bilateral acute pyelonephritis, bilateral ureteritis and necrotic cystitis with calculi, thrombosis of the vena cava and left ovarian vein, chronic cholecystitis and cholelithiasis, metastatic adenocarcinoma of the twelfth thoracic and third lumbar vertebrae. The uterus was normal. Study of the spinal cord revealed carcinomatous involvement of the epidural tissue and dural veins. The cord showed almost complete myelomalacia in the lower thoracic region together with ascending secondary degeneration.

SUMMARY

The present knowledge of the nerve control of the uterus is reviewed. A case is presented showing spontaneous painless parturition by decentralized uterus.

We are indebted to Mr. Gosner for the microphotography and to C. E. Lande for the drawings presented herein. We wish to thank Drs. H. E. Riggs, Benjamin Weiss, and F. B. Faust for their contributions to this case report.

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COMPLETE INVERSION OF UTERUS LATE IN PUERPERIUM

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THIS is a report of a case of late inversion of the uterus recognized twenty-six days post partum. It suggests that the process may not always be the sudden dramatic and shocking condition usually described but one occurring gradually as a misdirected aberrant involution. This adds to the already increasing number of such cases and thereby indicates that the process is not as rare as was formerly thought and that its late occurrence during the puerperium should be considered.

It was of interest to note that the uterus even following removal could not be reduced by forceful manual effort. The mucosal aspect of the inverted organ gave the impression of soft roughening and furring.

The photograph of the cut specimen showed the ischemia of the myometrium which had developed and the beginning necrosis of the endometrium both of which would make the reposition of the organ undesirable even if possible. It is possible that natural or traumatic weakness of the lower uterine segment, which is supposedly relatively thicker and stronger than the fundus, may play a part. There was no indication noted, it was stated by the attendant, of dimpling, flattening, or undue bleeding immediately after delivery.

This episode suggests to me that there is a possible reason for retaining the word "late" to describe this insidious, formidable, yet seemingly rare, complication of the puerperium. It further indicates that the contour of the fundus should be noted for several days post partum, and that the character of any bleeding during this period be investigated not only for the possibility of partially retained placenta and subinvolution but also for inversion.

The incidence of 1:400,000 in the primiparas or 1:200,000 in multiparas, as reported by Zangemeister, would seem to represent only the cases in the literature prior to his review of the subject in 1933. I do not presume to indicate any probable ratio but suggest that uterine inversion may be an ever present possibility and one to be considered and anticipated along with other accidents of the third stage and the puerperium. Spontaneous inversion during the involution of the uterus is possibly explainable by congenital developmental defects in the complicated anatomic structure of the uterus itself, particularly in the lower uterine segment; and resorption of the musculature by a low placental implantation. Atony of the uterine wall would easily allow this process to ensue. "Partial atony of the uterine wall is no doubt an indispensable condition for the inversion of the puerperal uterus" (Bock). Low placentation with thinning out of the myometrium may have been a predisposing factor. Normally coordinated uterine contractions in an intact uterus would hardly tend to develop such an accident. If one visualizes the natural ingenious heavy inner circular musculature, the obliquely downward spiral course in three directions of the outer layer of muscles (Piersol), it would seem possible that this condition could only supervene if traumatic or absorptive disruption had occurred.

CASE REPORT

Mrs. R., aged 22 years, gravida i, was delivered at the Kingston Hospital by outlet forceps and episiotomy of a normal living child weighing 5 pounds 5½ ounces on Oct. 10, 1940, following a sixteen-hour labor. There was no undue hemorrhage at the time of delivery of the child, and the placenta was expelled intact twenty-four minutes later. A low-grade febrile course accompanied by intermittent spells of bleeding was interpreted as being due to an atonic and subinvolved uterus. She was discharged on the seventeenth post-partum day. A blood transfusion of 500 c.c. was given during the puerperium as a general supportive measure. Questioning during the later puerperium at home elicited the story of continued slight bleeding, cramplike bearing-down pains, a sense of "dragging" in the hypogastrium and backache.

On November 4, twenty-five days post partum, this patient was readmitted to the Kingston Hospital with a completely inverted uterus. An unsuccessful attempt at manual reduction was made. The following day I was asked to see this patient in consultation.

On bimanual examination a spherical mass slightly larger than a baseball, though irregular and roughened, presented in the upper two-thirds of the vagina. No cervical rim could be found and the mass blended into the vaginal wall without any palpable interruption to the examining fingers. The left hand suprapubically through a relatively thin abdominal wall could feel no organ whatever, dimpled, flat, inverted or otherwise. The patient appeared ill and had a marked pallor. The pulse was thready, ill-sustained, and the rate was about 120. She had received 750 c.c. of citrated blood during the night and adequate doses of morphine. Hemorrhage had been only moderate since admission.

In view of the fact that reposition under deep anesthesia during the night plus the administration of epinephrine-hydrochloride (Daro) in an endeavor to relax the cervical sphincter had been unsuccessful, and since slight abdominal distention accompanied by a temperature of 102° F. had already developed, it was agreed upon that vaginal extirpation would be preferable. Blood count and hemoglobin determinations were 4,600,000 and 85 per cent, respectively, probably indicating increased capillary permeability and impending shock. Continuous and rapid administration of whole blood and plasma was begun. It was feared that a state of irreversible shock would soon develop. This was temporarily averted by the massive blood replacement, and in an hour it was felt that surgical treatment could be attempted.



Fig. 1.—Cut section of inverted uterus demonstrates hard irreducible consistency of the myometrium.

Under cyclopropane-ether anesthesia the uterus was withdrawn from the vagina en masse with surprising ease. Further attempt at reduction was obviously contraindicated due to the circulatory changes present. Introduction of a catheter showed that the lower portion of the bladder was drawn into the infundus of the uterus.

A vertical incision was made on the upper anterior surface of the prolapsed mass at the presumed level of the inverted bladder and down through the myometrium. The bladder was encountered immediately and with the index finger of the left hand was peeled upward and laterally thereby effecting satisfactory mobilization. The location of the ureters was obviously undeterminable. The tubes or ovaries were not drawn into the craterlike inversion. Double Kocher clamps were applied laterally at the same assumed level of and within the cervix, and a rapid removal of the herniated mass was effected with slight blood loss. The uterine arteries appeared thrombosed. Side-to-

side continuous hemostatic sutures were applied distal to the clamps and tight closure effected. There was notable absence of active bleeding during the procedure due to ischemia of the myometrium and the resultant degenerative change in the mural fibers. The mucous membrane of the vaginal vault was closed with a running stitch. The vagina was packed with iodoform gauze and a retention catheter placed in the bladder. The patient was returned to her room in fair condition. The immediate postoperative condition was relatively good. There was moderate shock treated by the usual measures and further transfusions. The response was good. Convalescence was uneventful though protracted. A low-grade septic course followed but with no definite pelvic peritonitis.

Examination on Jan. 15, 1941, revealed the vaginal vault well healed, the cervix small and unscarred, and the adnexa neither atrophic nor cystic.

SUMMARY

1. A case of complete inversion of the uterus recognized late in the puerperium is presented.

2. Ischemia and fixation of the tissue was sufficiently advanced to preclude reposition. The uterus could not be extraverted following removal.

3. The ovaries were not drawn into the crater, hence were not included in the extirpation.

4. The first step of the Spinelli procedure for replacement was utilized in mobilizing the bladder from the crater.

5. Low placentation with destructive effects on the lower myometrium is suggested by the given illustrations and offered as a possible contributory factor in the inversion.

6. Vaginal hysterectomy was necessary.

I wish to thank Drs. F. H. Snyder and J. B. Krom for the privilege of reporting this case.

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CHRONIC PUERPERAL INVERSION OF THE UTERUS*

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PUERPERAL inversion of the uterus is quite infrequent but not so rare as is generally believed. When the inversion is present three to four weeks or longer, it is regarded by Bland and Goldstein to be chronic. The latter is by far the least frequently encountered. The following is the clinical history of such a case:

L. H., white, gravida i, aged 22 years, had an uneventful prenatal course. She was admitted on June 16, 1941, to the hospital where she was delivered. The first stage of labor of fourteen hours was uneventful, and the second stage of nineteen minutes was aided by 2 min. of pituitrin. A normal male baby weighing 7 pounds 10½ ounces was delivered by episiotomy and low forceps. The placenta was delivered thirteen minutes later by "modified Credé," and a blood loss of "400 c.c." followed. Ergotrate 2 c.c., pituitrin min. XIII, and 750 c.c. of saline hypodermolysis were administered during the thirty-five minutes that followed the childbirth. A packing of 3 yards of gauze was also used to control the hemorrhage, and a 300 c.c. blood transfusion was given to the patient. Her condition was fair during the next twenty-four hours, but she had difficulty in voiding which persisted more or less until she was finally operated upon. On the fifth puerperal day, the episiotomy sutures began to slough, and a consultant was called to make a secondary repair. Her temperature had varied attaining a level of 101° to 103.4° F., and her pulse rate was 120 or higher. The consultant found a complete inversion to be present which had hitherto been unrecognized. The uterus could not be replaced, and he advised no further surgery until the patient's condition permitted. The patient received repeated transfusions, and sulfonamide therapy. The temperature gradually declined and was normal in about one week. She left the hospital by ambulance seventeen days after the delivery of her baby.

She had several hemorrhages at home and was admitted to the Cook County Hospital on July 26, 1941, forty days post partum with her vagina packed with gauze. The pack was removed in order to examine her and another was inserted. Her blood count showed hemoglobin 42 per cent, red blood count 2.55 and white blood count 4,500. In view of her poor condition, operative procedure was deferred until supportive measures, such as multiple blood transfusions, vitamin K, and an anti-anemic dietary regime were instituted. It was hoped that the uterus might involute further as the patient's condition improved. During the next seven days, the patient had 2 vaginal hemorrhages, and it was regarded unsafe to wait any longer. The second hemorrhage on the day preceding the operation was severe and necessitated a tight packing of the vagina, plus the injection of 500 c.c. of plasma, and 1,000 c.c. of citrated blood to improve her condition.

*Presented at a meeting of the Chicago Gynecological Society, November 21, 1941.

The patient was operated upon on Aug. 2, 1941. At this time the red blood count was 2.59 and hemoglobin 40 per cent. She was given a transfusion of 500 c.c. of blood during the operation, which was done under a light dose of spinal anesthesia reinforced by intravenous sodium pentothal. The uterus was considered to be too large for vaginal replacement by the Spinelli technique, therefore, the Haultain abdominal method was tentatively selected. Because of dense adhesions of the tubes and round ligaments to the peritoneal surfaces within the inverted pocket, it was necessary to incise the entire length of the uterus posteriorly in order to replace it. It was deemed wiser to remove this uterus, primarily because the edematous endometrium would necessitate much trimming and the uterus would then contain a sutured surface from cervix to fundus; secondarily, an infected uterus would be replaced into the peritoneal cavity of a patient whose resistance was certainly low; and finally, the hazard of such a scarred uterus for future gestation. A supracervical hysterectomy was easily done, and a Penrose drain was inserted into the dilated cervical ring. Four grams of sulfanilamide powder was placed into the pelvis.

The patient's postoperative course was stormy. On the fourth postoperative day the patient had a temperature rise to 105° F., and her pulse rate was 166. Thereafter, the temperature and pulse rate declined to normal. During the critical period of recovery the patient received several additional transfusions. She left the hospital on the sixteenth postoperative day, and when she was seen one month later, she had gained 10 pounds and appeared well.

The essential microscopic feature of this excised uterus was the replacement of the endometrium by a vascular granulation tissue.

PREGNANCY COMPLICATED BY ACUTE PERFORATED PEPTIC ULCER

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PEPTIC ulcer occurring with pregnancy is an exceedingly rare condition. Sandweiss, Saltzstein, and Farbman¹ found only one proved case of active peptic ulcer in 70,310 admissions of pregnant women to 5 Detroit hospitals during a ten-year period. In the same group of women numerous other gastrointestinal disorders, such as appendicitis, cholecystitis, and intestinal obstruction, were observed. These authors reported a case of a perforated ulcer in the anterior wall of the duodenum, occurring in a 42-year-old white woman (para x). The patient was in the sixth month of pregnancy when symptoms of extreme pain in the epigastrium and severe shock occurred. A differential clinical diagnosis of acute pancreatitis, perforated gastric ulcer, and ruptured gall bladder was advanced. The patient died shortly after delivery of a dead six months' fetus. The autopsy confirmed the diagnosis of a perforated duodenal ulcer.

Szenes² in a complete review of the European literature on the subject of peptic ulcer complicating pregnancy accepts only 3 cases in

which perforation of an ulcer or severe hemorrhage had occurred during pregnancy, or after delivery. The cases were confirmed by post-mortem examinations. One was in a woman (Chabannes' case³) in the fourth month of pregnancy in which perforation of a gastric ulcer occurred, also complicated by extensive tuberculosis of one kidney. A second case was that of Gminder⁴ in a 23-year-old female (para iii) who developed peritonitis eight days following delivery and died on the twenty-third day following delivery. At the autopsy two chronic peptic ulcers were found on the anterior and posterior walls of the stomach. Gminder⁴ felt that the ulcer on the anterior wall perforated during labor and the ulcer on the posterior surface perforated later following tremendous intake of fluid. The third case reviewed by Szenes² was that of Le Play,⁵ occurring in a 27-year-old woman who died in the seventh month of pregnancy due to hemorrhage from a large ulcer on the lesser curvature of the stomach. Mulsou and Brown,⁶ in 1936, described a case of fatal hemorrhage from a duodenal ulcer in a 41-year-old pregnant female. We wish to add another fatal case of acute perforated duodenal ulcer to the list of previously mentioned cases.

CASE REPORT

Mrs. B. S., a 29-year-old, white, married female, entered the Buffalo General Hospital on Oct. 28, 1940, with the following complaints: On the day previous to admission to the hospital, after an uneventful full-term pregnancy, the patient delivered a normal male infant. Following delivery an average amount of bleeding occurred, and the patient rested comfortably for several hours, when she noticed a dull pain in her abdomen and a sense of fullness. She had a desire to "move her bowels" and took several enemas and some castor oil. This procedure was followed by nausea and emesis of black material. Her past history was not enlightening. Two previous pregnancies had been uneventful. There was no history of previous surgery.

Physical examination revealed a seriously ill white female, somewhat cyanotic about the lips and cheeks and markedly dehydrated. The temperature was 103.8° F., pulse 120, and respirations 36. Except for the rapid heart and respiratory rate, the examination of the chest and heart was not remarkable. Blood pressure was 100/80.

The abdomen was markedly distended, tympanitic and slight tenderness was present. No spasm or rebound tenderness was elicited. Peristalsis was absent. The uterus was in the normal post-partum state. Cervix was dilated and no tenderness could be found on pelvic examination. The lochia was normal. Laboratory examinations, including urine, blood counts, and blood chemistry, were all within normal limits. A white count on admission was 8,100 cells per c. mm. of blood and on the second day after admission was 5,600 cells per c. mm. of blood. A flat x-ray film of the abdomen showed several distended loops of small bowel lying on the right side of the abdomen. Gas shadows were not observed in the pelvic region and the loops visualized were separated, suggesting that the apparent obstruction might be the result of a peritonitis or ileus. The admission diagnoses varied, including paralytic ileus, puerperal fever with septicemia, appendicitis, and peritonitis.

On admission the patient was transfused with 500 c.c. of blood and duodenal decompression was instituted, with favorable results. On the second day after admission the cyanosis increased and oxygen therapy

was instituted. The patient became more distended and increasingly restless and irrational. A second 500 c.c. of blood was given with continuous intravenous fluids, but the patient died at 1:47 A.M., Oct. 31, 1940 (fifty-four hours after admission). A blood culture report after death was negative for growth of organisms.

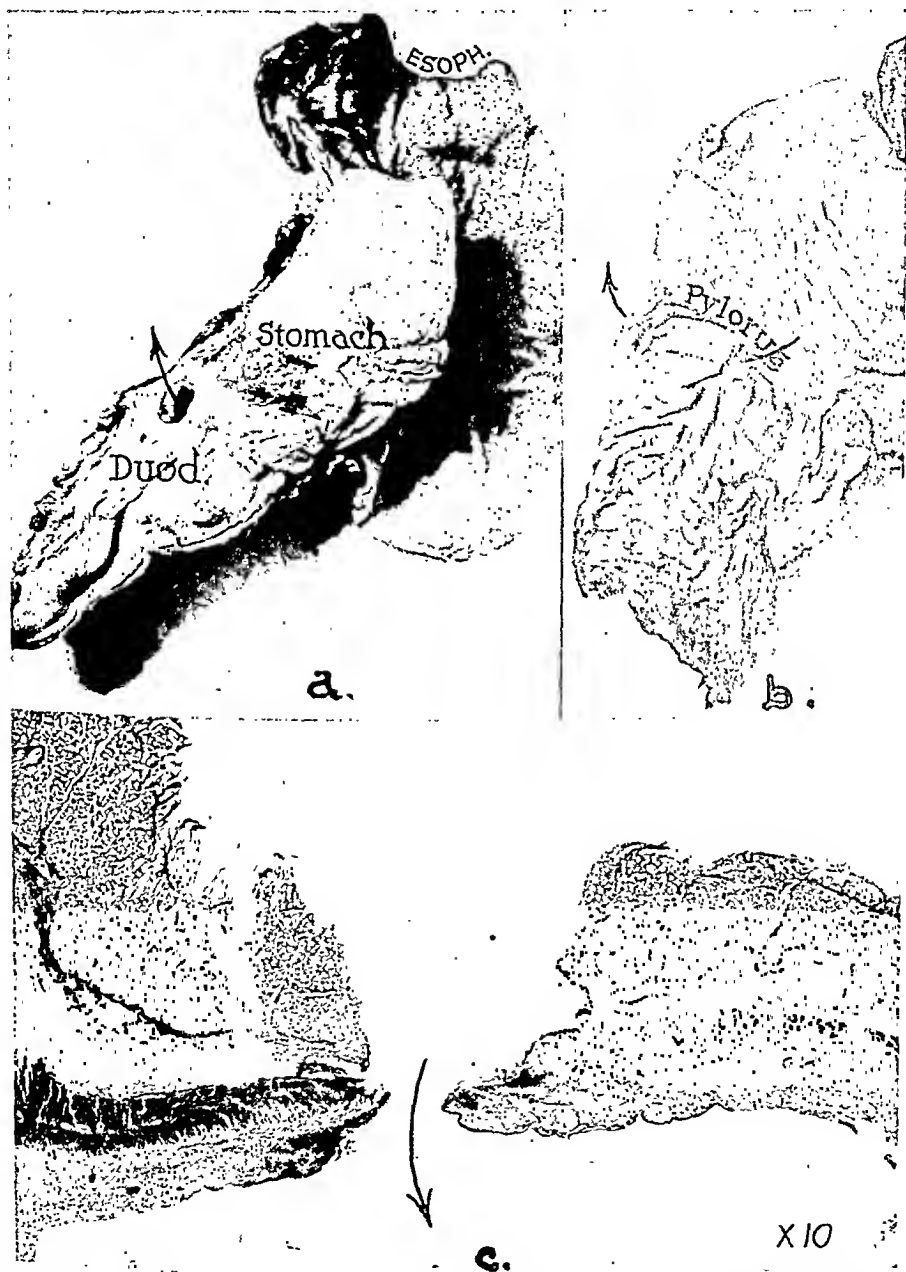


Fig. 1.—a, Anterior external view of the perforation of the acute duodenal ulcer. b, Illustrates a view of the mucosal surface of the stomach and duodenum. c, A cross section through the acute ulcer (stained with hematoxylin and eosin).

The autopsy was performed by Dr. Kornel Terplan and a summary of his findings follows:

“Markedly distended abdomen. A very large amount of fetid gas was found within the free peritoneal cavity. Diffuse fetid, serous,

purulent peritonitis, involving the entire peritoneal cavity and both subdiaphragmatic spaces, with at least 3 quarts of fetid, serous, dirty grey and slightly greenish fluid exudate, and with a pseudomembrane of about 2 mm. thickness completely covering all viscera in the peritoneal cavity, but especially the puerperal uterus and all the loops of small intestine which form a somewhat conglomerated mass. A perforated ulcer rotundum was found in the anterior wall of the first portion of the duodenum, measuring 1.1 cm. in diameter. There was complete disappearance of the original floor of the ulcer. A normal sized stomach, containing very little fluid, with scattered petechial hemorrhages in its mucosa and beginning post-mortal autolytic discoloration and superficial digestion were observed. Smears from the peritoneal cavity demonstrated a mixture of small gram positive cocci in short chains and many fusiform gram negative bacilli; also a few short gram negative bacilli, obviously of an anaerobic type."

The chief diagnosis was perforated round ulcer in the anterior wall of the first portion of the duodenum with recent diffuse, fetid, serofibrinopurulent peritonitis. In addition, a recent serous pleuritis with atelectasis of both lungs and a partially noninvolved puerperal uterus completed the autopsy findings.

The histologic findings of a section taken through the duodenal wall and the perforated ulcer are illustrated in Fig. 1. In both sides of the perforation the substance of the wall of the duodenum was almost completely destroyed. The borders showed very distinct effect of digestion and considerable inflammatory reaction. The absence of reactive changes in the duodenal mucosa in the area of the perforation was rather impressive. In the deeper areas of the submucosa, distinct evidence of inflammatory reaction, consisting of fibroblasts, lymphocytes, plasma cells, and relatively few leucocytes were found.

The muscle layers forming the border were covered by fibrinopurulent exudate. Inflammatory edema extended only for a short distance into the surrounding wall. The most marked inflammatory changes were seen in the subserosa with some extension into the outer serosal layer. The serosa was covered by a fibrinopurulent layer. There were autolytic changes within the muscle fibers bordering the perforation, accompanied by leucocytic infiltrates. A dense infiltration throughout the subserosa by plasma cells, fibroblasts, histiocytes, and a moderate amount of leucocytes was noticed. Capillaries were prominent and injected.

COMMENT

From the history in this case report, the perforation occurred a few hours after delivery. The patient developed peritonitis and died on the fourth day postpartum. Because of the more common gastrointestinal complaints of pregnant women following delivery, the possibility of peptic ulcer was not entertained as a possible diagnosis. Of course, as the symptoms of peritonitis appeared, the diagnosis of puerperal fever or a ruptured appendix was advanced. Numerous authors have called attention to the fact that peptic ulcer predominates in males, but even when peptic ulcer occurs in the female a beneficial effect of pregnancy on the symptoms of peptic ulcer has been observed. These beneficial effects have been observed by Roemheld,⁷ Szenes,² Sandweiss, Saltzstein, and Farbman.¹ Szenes² thought that the lowered acidity of

the gastric juice, the deposits of fat about the stomach, and the change of position of the stomach which improved the circulation of the lesser curvature of the stomach were factors in promotion of healing of ulcers in pregnant females.

The most impressive finding in the case was the small size of the peptic ulcer and its apparent acute and recent state. These conclusions were formulated by the extensive acute, inflammatory reactions at both sides of the perforation and the complete absence of fibrosis or even actual granulation tissue along the walls of the perforation.

In summary, another case of acute perforated duodenal ulcer complicating pregnancy has been presented and added to the three previously described cases in the literature.

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CARCINOMA OF BARTHOLIN'S GLAND

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CARCINOMA of Bartholin's gland is considered so rare that it is usually recognized too late to be successfully treated, and the diagnosis is seldom suspected before surgical intervention. Only 38 cases¹ were collected in the latest reported tabulation. However, Cosbie² found one carcinoma of Bartholin's gland in 57 cases of carcinoma of the vulva and in Taussig's³ series of 155 vulval cancers, 9 originated in the vulvovaginal gland. We report another case in which the condition was not suspected and which bore such striking resemblance to lymphogranuloma venereum that, regardless of repeated negative Frei tests, this remained as the clinical diagnosis.⁴

REPORT OF CASE

A negress, whose age was estimated at 65 years, was admitted on July 16, 1940, in a state of cardiac decompensation and mental cloudiness. The unsatisfactory history with reference to the vulval lesion was obtained from a daughter. Four years previously an abscess of the hip was incised and afterwards the process spread. One or two years prior to admission a sore appeared on the vulva. The physical examination and necropsy findings exhibited no relation between the vulval mass and a lesion of the hip.

Her terminal illness began one month ago with swelling of the lower extremities which was soon followed by edema of the hands and arms. Members of her family had noted indistinctness of speech and mental cloudiness for two weeks. The family history was negative for cancer. Venereal infection was denied. The patient had three daughters and one son, all in good health. The menopause occurred at an undetermined previous age.

Examination of the vulva revealed some edema of both labia majora, and pronounced enlargement of the left. The swelling on the left extended posteriorly to involve the buttock to the level of the coccyx. This tumorlike mass was irregularly ulcerated, and in the perineum there were several deep sinuses which discharged mucopus. Inguinal lymph nodes were not palpable. Intradermal tests with three different brands of Frei antigen were negative and no reaction followed the intradermal injection of chancroidal vaccine. The Wassermann and Kahn reactions on the blood were negative.



Fig. 1.

Generalized edema, weak heart sounds, and a low blood pressure indicated a terminal stage of congestive heart failure. Hemoglobin (Osgood-Haskins) measured 5.0 Gm. There were 3,900,000 red blood cells and 13,200 leucocytes per c.mm. of blood. The urine contained albumin, 2-plus. The patient did not respond to therapy directed toward the failing heart and died rather suddenly on the fourth day of hospitalization.

Necropsy confirmed the clinical impression of congestive heart failure. There was generalized arteriolar sclerosis. The heart weighed 445 Gm., and there were scattered areas of fibrosis in the myocardium. A large mural thrombus was attached to the apex of the right ventricle. Four small red infarcts were present in the right lung from embolic occlusion of the arteries and three of the large branches of the pulmonary artery on the right and two on the left were almost occluded by emboli. Subcutaneous edema was generalized. The peritoneal cavity contained about

1,000 c.c. of clear fluid, the right pleural cavity, 1,000 c.c., and the left 500 c.c. The pericardial cavity was distended with approximately 100 c.c. of clear fluid. Chronic passive congestion of lungs, liver, and spleen was evident. Incidentally, a small myoma was present in the anterior wall of the stomach, and in the mucosa of the duodenum there was a minute accessory pancreas.

The dorsal three-fourths of the left labium majus was enlarged and projected as a mass 18 cm. long and 9 cm. broad, which extended dorsally to the level of the coccyx. The surface was irregularly ulcerated and numerous sinus tracts discharged mucus. On section the mass was composed of numerous locules filled with thick stringy mucus. The locules varied in size from minute ones to 1.5 cm. in diameter and were separated by delicate fibrous strands. There was no capsule. The inguinal nodes were not enlarged and on section no metastases were found.

Microscopically the newgrowth was composed of glands and locules which were generally lined with a single layer of columnar epithelium. All of the locules were filled with mucus, and in some the surface was denuded of epithelium, either in whole or in part, and from these, mucus had escaped into the interstitial tissue. The glands and locules were supported by narrow and broad bands of connective tissue. At the sites of ulceration leucocytic infiltration indicated infection (Fig. 1).

DISCUSSION

In an excellent review of the literature, Simendinger,¹ in 1939, was able to collect only 38 cases of primary carcinoma of Bartholin's gland. Of these 29 were adenocarcinomas and 9 were squamous cell carcinomas. The latter presumably arose from the duct. He stated that most authors agreed that metastases to the inguinal lymph nodes occurred early. Falls⁵ and Strauss⁶ mentioned that metastases were frequent and recurrence common, and Hunt and Powell⁷ reported a poor prognosis in malignant disease of Bartholin's gland. However, Mayo and Barber⁸ found that in their three patients, the tumors were of low-grade malignancy and that metastases occurred slowly. They attributed the unfavorable prognosis to uniform failure of early diagnosis. Lyle,⁹ Falls⁵ and Strauss⁶ also commented on the fact that early diagnosis was seldom made and Rabinovitch¹⁰ thought that the common source of failure of surgical procedure was the surgeon's inability to recognize at operation the malignant character of the neoplasm. Taussig³ has aptly stated that "in no form of genital cancer do we find more evidence of inexcusable delay in seeking medical advice than in cancer of the vulva. This delay is only too often increased by failure in diagnosis or improper advice on the part of the family doctor."

The majority of cases occurred between 40 and 55 years of age. Simendinger¹ and Hoffmann¹¹ did not consider infection a predisposing factor. On the other hand Harer¹² thought that chronic inflammation (non-Neisserian) was probably a predisposing cause and observed that no cases had been reported in virgins. Falls⁵ stated that chronic inflammation had been present in a considerable number of the reported cases, and in the case reported by Taussig,¹³ the carcinoma followed trauma. In his later report³ he found that infection was definitely present in 4 out of 9 Bartholin gland tumors.

Our case appeared to be of low-grade malignancy, and although the local tumor was far advanced, no metastases were found. It appears to us that various gradations as to rate of growth and the rapidity of metastasis would be present here as in carcinomas of other organs. This would depend on the degree of anaplasia. This case is also of interest because of the striking resemblance of the lesion to lymphogranuloma venereum. However, this resemblance is superficial and careful examination of the site should have indicated the differentiation. In the vulva the "elephantiasis" was confined only to one labium majus and did not involve the labium minus. It was also unilateral. These observations together with the repeated negative Frei test should have eliminated the possibility of lymphogranuloma venereum.

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RUPTURE OF THE SCAR OF A LOWER SEGMENT CESAREAN SECTION WITH TRANSVERSE INCISION

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IN RECENT years, obstetric interest has become more and more focused on the lower segment two-flap cesarean section with a transverse incision. The transverse incision has been known for many years especially through the work of Kerr, but has become more popularized lately by Marshall¹ in England and Phaneuf² in the United States. The arguments for and against the use of the transverse incision have been excellently discussed in Marshall's book on the subject.

One of the chief fears of obstetricians with regard to the transverse incision seems to be that of rupture. Nevertheless a perusal of the literature reveals only one reported case of rupture of the scar of a transverse incision in a subsequent labor. This was reported by Sheldon³ from Irving's clinic. In addition Irving⁴ has four other similar cases as yet unreported. These same five cases are also mentioned in Marshall's book. Unfortunately, due to lack of published statistics, there is no way of arriving at the incidence of rupture of the uterus following this technique. However, the fact that only five cases can be dis-

covered of rupture of the scar of the transverse incision would seem to indicate that the danger is minimal.

For the past four years the obstetrical service at Cumberland Hospital has adopted the use of the transverse incision as the procedure of choice. During this time, 46 such operations have been performed. Recently we encountered a case of spontaneous rupture of the scar of the transverse incision in one of our own cases. This we are reporting in detail.

CASE REPORT

I. R., aged 24 years, colored, gravida ii, para i, was admitted to the Cumberland Hospital, Dec. 24, 1939, on the service of Dr. A. E. Dunbar, complaining of weak labor pains of one and one-half hours' duration. Her expected date of confinement was Dec. 12, 1939. She had previously been delivered on Nov. 11, 1938, by a lower segment cesarean section with transverse incision for cephalopelvic disproportion following a thirty-six-hour labor with intact membranes. Her post-partum course was complicated by an endometritis of six days' duration. The patient also had been receiving antisyphilitic therapy.

Examination on admission disclosed the abdomen soft, fundus to be at term, fetus in the L.O.A. position, and the fetal heart of good quality in the left lower quadrant. Rectal and vaginal examinations were not done. Pains began about one hour before admission, continued every ten minutes, and were moderately strong. The membranes were apparently intact.

The patient was immediately prepared and taken to the operating room. Under local infiltration of 1 per cent procaine, a lower segment two-flap cesarean section with transverse incision was performed with delivery of a living male child. The placenta was removed manually.

Examination of the uterus preparatory to suturing the transverse incision revealed a second transverse opening into the uterine cavity about one and one-fourth inches below the new uterine incision. There was no evidence of bleeding from the edges of this opening which showed a firm glistening surface. Because of the absence of hemorrhage and the apparent scarification of the lower end, the opening was interpreted as a spontaneous rupture of the old transverse incision. Due to the difficulty of re-suturing the laceration, a hysterectomy was done. The uterus was amputated at the level of the site of the apparent rupture. The operating time was one hour and thirty minutes. General anesthesia of nitrous oxide and oxygen was given at the time hysterectomy was decided upon. The postoperative course was entirely uneventful and mother and child were discharged in good condition on the fourteenth day post partum.

Pathologic Report by Dr. S. Polayes.—Microscopic examination of sections through the anterior wall in the line of amputation showed the endometrium to be composed of decidual cells. The myometrium was partially replaced by scar tissue and contained areas of old hemorrhage. The sections corresponding to the recent incision showed no scarification and a few areas of fresh hemorrhage.

DISCUSSION

An interesting feature of this case was the absence of any symptoms or signs of rupture of the uterus. Because of the operative findings and

the pathologic report, we feel warranted in drawing the conclusion that the rupture was spontaneous and occurred before labor began.

Further study seems to indicate that the post-partum febrile course following the original section was the underlying factor responsible for the improper healing of the lower segment scar and its subsequent spontaneous rupture. Undoubtedly, too, the concurrent syphilis played a part. It is the experience of obstetricians in general that post-partum infection following cesarean section by any technique is the chief etiologic factor in subsequent rupture of the scar.

Experience has shown that supraeervical hysterectomy is the procedure of choice in the treatment of rupture of a scar following section. The uneventful post-partum course of the case presented is in keeping with this.

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960 STERLING PLACE
868 PROSPECT PLACE

PROLAPSUS UTERI ASSOCIATED WITH SPINA BIFIDA AND CLUBFEET IN NEWBORN INFANTS

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IN 1927 Noyes¹ reported a case of uterine prolapse associated with spina bifida in the newborn infant. He also reviewed the literature up to that date and found 24 similar cases, each of which he abstracted. Most of the babies died within the first month after birth. Noyes' conclusions are as follows: "A review of the cases reported leads one to infer that the spina bifida is the primary etiologic factor in the occurrence of the prolapse. It would appear that if certain of the sacral nerves are drawn into the spina bifida, there is a partial or complete paralysis of the musculature of the pelvic floor resulting in secondary atrophy.

"On account of the high mortality in cases of spina bifida aperta, uterine prolapse associated with this condition is of little practical interest, but, inasmuch as present methods of diagnosis prove that spina bifida occulta is much more frequent than was previously suspected, a thorough search for this condition in all cases of uterine prolapse in which the etiology is not evident may throw some light on the subject.

"Ebeler and Duncker state that a study of 28 cases of uterine prolapse showed spina bifida occulta in 28 per cent, whereas an equal number of women without prolapse showed the condition in only 10 per cent. Further investigation of this interesting phase of the subject would seem to be warranted."

Ten years previously Palmer Findley,² writing on prolapse of the uterus in nulliparous women, had stated that in such cases it occurred most frequently in the newborn infant and in most of these instances was associated with congenital defects, notably spina bifida. He noted that the uterine prolapse was rarely evident at the time of birth, but developed during the first week. Such was the condition in the case reported in this paper.

From the literature, Findley found numerous associated lesions in the newborn cases, i.e., hydrocephalus, ankle clonus, clubfeet, scoliosis, kyphosis, flat or perpendicular pelvis, infantile uterus, flat and shallow vagina, elongated cervix, prolapse of rectum, inguinal hernia, paresis of perineal muscles and disturbed sensation in the lower extremities.

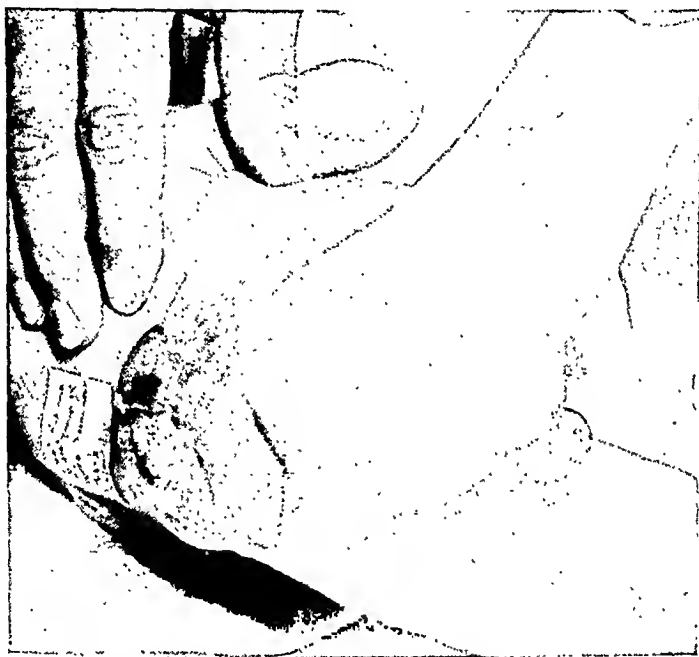


Fig. 1.—Showing infant with spina bifida tumor and prolapsed cervix.

Not all cases of spina bifida in the female infant are associated with prolapse of the uterus. Coughlin³ reported operations upon 12 infants, of whom 7 were females, in none of whom was there prolapse of the uterus, although bowel and bladder paralysis were frequently noted and in some cases there were clubfeet.

Uterine prolapse occurring later in life in the nullipara may be associated with occult spina bifida. If it comes early, the association is more common.

Pollock⁴ reported cervical and vaginal prolapse in a negro prostitute, 13 years of age, and this was not associated with spina bifida occulta as shown by x-ray; but she did have scoliosis of the thoracic spine, protuberant abdomen, and genu valgum.

Brocq and Beclerc⁵ reported the case of a 30-year-old woman in whom x-ray studies revealed bicornate uterus and spina bifida occulta of the fifth lumbar vertebra. Apparently there was no uterine prolapse.

Von Graff⁶ found 2 of 4 nulliparous women with uterine prolapse to have spina bifida occulta when examined by x-ray, and a third one suspicious of such defect. Among nulliparous women with prolapse he found about one-half to be of the "asthenico-ptotic" constitutional type of individuals with congenital weakness and looseness of the mesodermal tissues. These may develop prolapse of the uterus, which is a hernia of the pelvic floor, under stimulus of recent labor.

Laws⁷ studied 3 multiparas with early occurrence of prolapse after operation, and all three had definite spina bifida occulta. He, however, repeated Ebeler's study of 25 parous women with prolapsus uteri, and only one had spina bifida occulta.

CASE REPORT

Newborn, white female infant, rather cyanotic at birth, but well nourished and weighing 6 pounds and 3 ounces, was apparently normal, except for a spina bifida tumor over the lumbar region which consisted of a fleshy mass about 3 inches long and 1½ inches across and covered with some purulent exudate on the dorsal surface. In addition, the infant had bilateral talipes varus (Fig. 1). At the sixth day, it was first noted that "there is a protruding mass from the vagina about 1 inch in diameter with opening in the center shown to be the cervix." As the child progressed this mass receded into the vagina somewhat. The urethra and bowel tract were normal. Although by the nineteenth day the infant had taken nourishment well enough to weigh 7 pounds and 2 ounces, she had fever from 100° to 103° F. each day, probably due to infection of the surface of the raw spinal tumor. The infant had normal red blood count and normal hemoglobin and leucocytosis of 15,300. The urine was normal.

On the twenty-seventh day it aspirated some milk, and thereafter was cyanotic and probably developed pneumonia, causing its death on the twenty-ninth day. Post-mortem examination was refused.

The mother was a normal white primipara, aged 18 years, and the father was normal and aged 22. There was no history of congenital anomalies in either family.

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Five women diabetics of menopausal age were given 1 mg. of diethylstilbestrol four times daily for eight weeks. The changes noted were not greater than the normal variations in diabetes. The results were so consistently negative that even though the series was small it seemed significant.

CARL P. HUBER.

PREGNANCY COMPLICATED BY HODGKIN'S DISEASE

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HODGKIN'S disease and pregnancy form a rather unusual combination, a recent report by Kushner¹ stating that only three cases have been reported in the literature. Although Jemmell² reported only one case, he gives references to 13 reports in which further cases are mentioned. In most of the other instances, the Hodgkin's disease existed before the patients became pregnant, was chronic in type, and terminated fatally after rather long periods of time. The shortest time elapsing between delivery and death was one hundred ninety days. In the case here reported the pregnancy had progressed to approximately twenty-four weeks before the Hodgkin's disease asserted itself.

CASE REPORT

Mrs. A. M., a primigravida, aged 33 years, first consulted me on April 16, 1941. Her last menstrual period began on Jan. 15, 1941; the expected date of delivery, therefore, was Oct. 22, 1941. The past history was negative except for a long existing eczema of the skin of the entire body with itching. Physical examination, Kahn test, and urinalysis were all negative except for the finding of an early pregnancy.

The gestation progressed satisfactorily, and the patient's complaints were insignificant until Aug. 1, 1941, when she appeared for her regular prenatal visit, complaining of a swelling in the right inguinal region. This was found to be a chain of enlarged glands, each about the size of a hazelnut. No other glands in the body were found to be enlarged at that time, and there was no local lesion which could have been responsible for this adenopathy. A white blood count on that day revealed 11,000 leucocytes with a normal differential distribution and without eosinophilia.

Two weeks later the glands had doubled in size and there were small glands in the left inguinal region and in both axillae. The patient had developed a definite weakness. Two weeks later the condition appeared to be progressing further with the right inguinal glands again having doubled in size. Biopsy was advised.

On September 5, the patient was hospitalized and a biopsy performed by Dr. S. Perlow. Microscopic examination of the removed tissue revealed an early Hodgkin's lymphogranulomatosis (Dr. I. Davidsohn). By this time the patient had developed a severe cough and her general condition was becoming worse. Roentgenogram of the chest revealed no abnormalities. The pregnancy was developing normally. Roentgen ray treatment of the glands was advised, but owing to the proximity to the developing fetus, the dosage was necessarily small, and screening heavy.

In spite of this treatment the glands in the right inguinal region continued to enlarge. The size of this gland mass, the cough, the respiratory difficulty apparently aggravated by the growing pregnancy, and the progressive weakness made it impossible for the patient to move around, walk, or sleep. On September 30, she was re-admitted to the hospital with the right inguinal glands the size of two fists and a beginning edema of the vulva. Blood check-up showed 21,250 leucocytes, 5,410,000 erythrocytes, and 71.4 per cent hemoglobin. The patient was typed and suitable donors secured.

The edema of the vulva progressed so markedly and so rapidly that induction of labor was deemed inadvisable. At the same time emptying of the uterus was rather imperative for the comfort of the patient and in order that massive roentgen ray treatment could be begun.

On October 7, a low fundal cesarean section was performed under ethylene-oxygen anesthesia. A female infant weighing six pounds fourteen ounces was delivered. Thorough examination of the infant revealed no abnormalities. In the mother, chains of enlarged periaortic glands were palpated up to the diaphragm on both sides.

The postoperative course was uneventful and the vulvar edema rapidly subsided. Massive roentgen ray therapy was begun as soon as it was felt that the wound was sufficiently healed. The condition of the patient became progressively worse, with elevation of temperature and no decrease in the size of the glands. Death occurred on November 22, forty-five days after the delivery of the baby.

Autopsy confirmed the pathologic diagnosis of Hodgkin's disease.

Extensive comment is omitted here because the many unusual features presented by this case are worthy of a more detailed study and report which will be made subsequently.

It might be well to summarize the more interesting features noted in the study of this case:

1. The apparent onset of Hodgkin's disease during the second trimester of pregnancy.

2. The rapidity with which the disease proved fatal.

3. The manner in which the pregnancy and apparently the baby were entirely unaffected by the Hodgkin's disease.

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310 SOUTH MICHIGAN AVENUE

TREATMENT OF CERVICITIS WITH NEGATAN (NEGATOL)

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ONE of the problems that confront a gynecologic clinic is the treatment of cervicitis. Cauterization of the cervix can successfully cure most cases. However, there are times when cauterization is either contraindicated or not available. As a substitute, the topical application of chemicals to the cervix in the treatment of cervicitis has led to such disappointing results that such therapy has virtually been suspended in the gynecologic clinic at Bellevue Hospital.

However, during the year 1938 a new preparation, Negatan (Negatol), was employed in the gynecologic clinic at Bellevue Hospital. As a result of a preliminary survey done during that year, it was concluded that the drug had shown such merit that it warranted further and more intensive investigation. Simultaneously with the clinical studies, K. K. Chen, of the Research Laboratories of Eli Lilly Corporation was determining the chemical and pharmacologic nature of the drug.

With the permission of Dr. Chen, his statements are quoted:

"Negatol is the condensation product of *m* cresol sulfonic acid and formaldehyde diluted with sufficient water to give a specific gravity of 1.17 to 1.18. This constitutes a 100 per cent strength. For experimental purposes dilutions can be made from it by volume. It is brown-black in color, and is definitely acid to litmus. A 10 per cent solution measures a pH value closely equivalent to that of N/10 solution of hydrochloric acid. It has an empyreumatic odor not unlike that of cresol. It possesses a strong coagulant action, precipitating dilute solutions of egg albumen and various alkaloids, such as ephedrine, atropine, strychnine, aconite, quinine and nicotine.

"Although Negatol is recommended for local application in gynecological practice, its toxicity has been determined in small animals by internal administration. The median lethal dose of a 10 per cent solution in mice by intravenous injection is 3.198 ± 0.166 c.c. per kg. of body weight.

"Rats tolerate oral feeding of 0.4 c.c. of a 10 or 20 per cent solution of Negatol daily, except Saturday and Sundays, for a period of eight weeks. There is a slight inhibition of growth towards the end of the experiment. No pathological lesions can be demonstrated in the gastro-intestinal tract or parenchymatous organs.

"Local application of Negatol to rabbits' eyes or dogs' noses is followed by irritating effects.

"Repeated painting of higher concentrations (50 or 100 per cent) of Negatol on human skin occasionally results in a burning sensation, erythema, and superficial desquamation. It is, however, well borne by the majority of individuals.

"Repeated application of Negatol to dogs' vaginal walls and cervix, consisting of painting with a 10 or 20 per cent solution and insertion of a tampon saturated with 100 per cent Negatol, may be followed by congestion and excessive secretion if it is

made daily. When the medication is limited to twice a week, no pathological changes can be detected in the vaginal canal or cervix of uterus at the end of the eighth week. Only in one instance has a focal ulceration been observed.

"When injected intravenously in etherized cats, Negatol causes a fall of blood pressure with acceleration of respiration.

"No evidence has been obtained to show that Negatol is absorbed from mucous membranes, skin or extravascular tissues."

It is to be emphasized that the purpose of the present study is to evaluate the therapeutic efficacy of negatan in the treatment of cervicitis. No attempt was made in this investigation to compare the effect of Negatan with other methods of treatment.

Cervicitis cases were classified into five groups, after the classification of H. B. Matthews:*

- Class 1: Superficial erosion of recent duration.
- Class 2: More extensive erosion of longer duration.
- Class 3: Extensive erosion of long duration.
- Class 4: Extensive erosion with eversion, laceration, and Nabothian cysts.
- Class 5: Limited to endocervicitis alone.

Obviously, even such a classification has its drawbacks because of individual interpretation. Each doctor, on examining a patient, was asked to draw on a specially mimeographed chart the extent of the erosion.

The following outline describes the method of treatment:

Patients with cervicitis returned twice a week for treatment, at which time the vagina was cleansed, the cervical erosion was painted with 100 per cent negatan, and a gauze wick, the proximal portion of which was dipped in 100 per cent negatan, was placed in the cervical canal. The wick was held in place by a dry, vaginal tampon which was removed in twenty-four hours and followed by a cleansing vinegar douche. It must be stated that frequently patients did not return as often as twice a week for treatment, sometimes as long as one or two months elapsing between treatments. However, in the statistical compilation on the duration of treatment, there was no way of correcting for the factor of irregularity of visits.

The results obtained in the treatment of cervicitis are shown in Table I.

TABLE I

CLASS	CURED	DURATION NO. DAYS	AVE. NO. TREAT- MENT	IMPROVED	DURA- TION NO. DAYS	AVE. NO. TREAT- MENT	FAILURE	AVE. DURATION NO. DAYS	AVE. NO. TREAT- MENT
1	43	35	5.0	6	32	4.5	2	59	8
2	67	48	6.0	32	35	4.0	1		
3	35	61	9.5	29	58	6.1	5		
4	10	79	9.7	11	43	5.0	2		
5	14	41	5.5	0	0	0	3		
169 (65%)				78 (30%)			13 (5%)		
Total number of cases, 260									

*Am. J. Surgery 26: 233, 1937.

Cases were termed "improved cases" if a study of the drawings revealed a considerable lessening of the extent of erosion. Even if the "improved cases" were placed in the "failure" column; because an ultimate cure had not been obtained, a 65 per cent cure of cervicitis by the topical application of a chemical to the cervix is most impressive. It is apparent from Table I that the more severe the erosion, the more treatments it required, and the longer time it took to effect a cure. In none of the patients treated were there any untoward reactions. It was noted during the course of our investigation that negatan could be effectively used as a hemostatic agent. Consequently, it found use in post-cautery bleeding of the cervix, traumatic bleeding of the cervix as tenaculum puncture wounds following a tubal insufflation, and even in those cases of moderately profuse bleeding from cancerous lesions of the cervix.

In conclusion, an evaluation of the results obtained in the treatment of 260 cases of cervicitis with this preparation permits us to recommend its use in those cases of cervicitis where cauterization is either contra-indicated or too hazardous a procedure.

Albert, M.: Massive Adrenal Carcinoma With Pseudohermaphroditism, Brit. M. J. 2: 265, 1941.

The author reports the case history of a two-year-old female infant with an adrenal cortical carcinoma. The child's mother complained of the infant's fretfulness and abdominal swelling over a two-week period. Physical examination revealed a thin puny infant showing axillary and pubic hair growth of male distribution. The clitoris was enlarged with a small glans. Rudiments of a prepuce were visible. An enormous ovoid, smooth, hard mass was palpable in the right abdomen, bulging the right flank outward from the costal margin to the iliac crest. The mass did not move on respiration. A diagnosis of massive adrenal cortical tumor with pseudohermaphroditism was made. Laparotomy revealed a right adrenal tumor 9 by 6 inches in diameter. Enlarged para-aortic glands were removed for section, and the abdomen closed. The child's general condition rapidly deteriorated and she died the following day.

Post-mortem examination revealed the left adrenal gland and kidneys to be normal. No evidence of metastases was found in the liver. The uterus was very small and the ovaries were small fibrotic nodules.

Histologically the report showed "a cellular malignant tumor with the character of a carcinoma of the suprarenal cortex. Details are more distinct in the gland specimen as the tumor itself is the site of extensive necrosis."

The article discusses briefly the alteration of sex characters by hormonal imbalance due to adrenal gland changes. Excessive cortical sterone in the female before the onset of female sex characters may result in pseudohermaphroditism and the onset of excessive hormone after puberty may result in adrenal virilism. In the male, excessive sterone may cause feminism.

FRED L. ADAIR AND WILLIAM ROSENBAUM.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology

The ninth edition of the now classic textbook of *Diseases of Women*¹ by H. S. Crossen and R. J. Crossen has appeared. This edition continues to show improvement throughout in its presentation of the fundamentals of gynecology. All in all it is one of the most informative treatises for the practitioner, as well as for the specialist, because of its accuracy, the careful arrangement, and the concentrated presentation of facts. In spite of its being kept fully up-to-date, the increase in number of illustrations by sixty-nine, and the addition of a bibliography of twenty-three pages, the volume is fifty-one pages shorter than the previous edition. This difficult task has been accomplished by meticulous sifting and condensation. In this edition, special emphasis has been placed on the physiologic aspects of diseases.

R. T. FRANK.

Novak's *Gynecology and Female Endocrinology*² is designed primarily for the general practitioner and medical student. It covers both of these fields in a fairly exhaustive fashion, conforming in most ways to the usual standard textbooks. While diagnosis and treatment have been featured, all operative details have been purposely and wisely omitted. The text is concise and clear. The endocrine mechanism of menstruation and pregnancy is very well presented. The discussion of physiologic tumors of the ovary likewise deserves commendation for its clear-cut exposition.

A main feature is played by the abundant and exceptionally good illustrations. For gross illustrations, many are borrowed from classical sources, with due credit to the source; the microscopic illustrations are mainly from the collection of the author and are numerous, well chosen and most beautifully executed. In addition there are a number of handsome colored plates. Each chapter is concluded with a short, well-selected, useful bibliography.

Of the more than 600 pages, 445 are devoted to gynecology, the remainder to endocrinology. The present trend to overemphasize organotherapy, rather than endocrine diagnosis, is unconsciously evidenced by the fact that the chapters on endocrinology begin with "General Principles of Gynecological Organotherapy." The author shows a more marked trend toward conservative therapy in endocrinology than he has heretofore. He overemphasizes, in my opinion, the applicability and value of suction biopsy as may be seen from the following: Under the heading of "Occasional Therapeutic Value," he states that "As with ordinary curettage, functional bleeding may be cured by suction curettage." Nor can we agree with the statement that "It is probable that certain endometria are refractory to the growth

¹*Diseases of Women*. By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology, Washington University School of Medicine, etc., and Robert James Crossen, Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Ninth edition, entirely revised and reset. 948 pages with 1127 engravings, including 45 in color. The C. V. Mosby Company, St. Louis, 1941.

²*Gynecology and Female Endocrinology*. By Emil Novak, Associate in Gynecology, the Johns Hopkins Medical School, etc. 605 pages with 425 illustrations, many in color. Little, Brown and Company, Boston, 1941.

effects of estrogen. . . .” The multiple subdivision of causes of both menorrhagia and amenorrhea appear hardly warranted in the present state of our knowledge. The chapter on sterility, which includes both the male and female, is excellent. It might have been wise to emphasize even more strongly that lipiodol hysterosalpingography must be limited to patients whose tubes have already been proved nonpatent by means of the insufflation test. The volume is concluded by a chapter on pregnancy conditions in gynecologic practice.

R. T. FRANK.

Obstetrics

A new monograph, *Preeclamptic and Eclamptic Toxemia of Pregnancy*,³ by Lewis Dexter and Soma Weiss, analyzes this problem by a physiologic approach. The recent untimely death of Dr. Weiss is greatly lamented in the loss to American medicine of his brilliant mind.

Among the various clinical and pathologic phases investigated were edema, changes in arterial pressure and other factors of hemodynamics, and function of the kidneys. In discussing the findings of these investigations, the authors have sought to interpret recent literature in the light of their own results. By exclusion, a primary humoral etiology of generalized edema in pregnancy is suspected. No significant relationship between posterior pituitary and hypertension of late pregnancy could be adduced, nor could the toxic reactions of this pituitary be regarded as similar to toxemia of pregnancy. The authors were unable to determine the presence of a pressor substance (renin) in the placentas of hypertensive pregnant patients. A circulating pressor substance, if present in the mother, apparently does not cross the placenta to affect the infant similarly. Hormones were not found to produce a syndrome comparable to human toxemia in experimental animals, and pregnancy in animals evidently does not accentuate hypertension induced by renal ischemia.

In discussing the clinical and pathologic features of pre-eclampsia and eclampsia the authors have exhaustively studied 80 such cases with special reference to hypertension antedating pregnancy. The results of these clinical and laboratory studies again have been compared with a large group of similar studies in recent literature. The pathology of renal changes in eclampsia and infections and the degenerative lesions are well illustrated. There is an excellent section on cortical necrosis and another on vascular collapse in eclampsia. The various theories of etiology are carefully analyzed. The classification of the toxemias of pregnancy offered by the American Committee on Maternal Welfare is regarded as mildly unsatisfactory, at least, on grouping. The immediate renal lesion of eclampsia is regarded as a glomerulonephrosis. The authors feel that while no specific “toxin” has been found responsible the placenta must be regarded as the “intrauterine factor” responsible, although the pathogenesis is due to multiple rather than to single operative factors. They offer a diagrammatic representation of their conception of the factors involved. There is a significant suggestion that the relationship of isoimmunization and isoagglutinins has not been sufficiently studied.

The various methods of treatment are dissected, many are discarded, some are recommended. Aside from prenatal care and practice of preventive measures, reduction or prevention of edema, and of sodium retention in the tissues is regarded as the most important single principle involved.

This monograph will greatly interest not only the clinical obstetrician but as well the internist and the physiologist, one from the medical, the other from the research aspects presented.

PHILIP F. WILLIAMS.

³*Preeclamptic and Eclamptic Toxemia of Pregnancy*. By Lewis Dexter, M.D. Research Fellow in Medicine, Harvard Medical School, and Soma Weiss, M.D., Hersey Professor of the Theory and Practice of Physic, Harvard University, etc. In collaboration with Florence W. Haynes, Herbert S. Sise, and James V. Warren. 415 pages with 44 illustrations. Little, Brown and Co., Boston, 1941.

Dieckmann, an outstanding contributor for years to both the clinical and research aspects of the toxemias of pregnancy, offers a new monograph, *Toxemias of Pregnancy*,⁴ on the subject. The book has been written with two objectives in mind: to acquaint the obstetrician with some of the recent contributions on physiology pertaining to obstetrics, and to acquaint the investigator, untrained in obstetrics, with some of the physiology and pathology of obstetrics.

As to classification of the toxemias, the author discusses the grouping offered by the American Committee on Maternal Welfare. He feels that no case should remain unclassified, even if the diagnosis has to be changed at a later date. A study of the factors influencing incidence leads to the conclusion that high average temperature, small range of temperature, and high measure of rainfall are of importance. The section on Pathology brings together the contributions of Bell and Page, and others, on studies of the glomerulus.

The section on Normal and Abnormal Physiology covers a wide range of subjects. The author regards the decrease in blood and plasma volume in the eclampsias a finding which precedes the clinical symptoms, as an important factor. Attention is directed to factors which may initiate or intensify blood concentration. The position is taken that a hypoproteinemia does not cause the eclamptic conditions, nor the accompanying edema. The changes in many of the blood constituents seen in eclampsia, blood sugar, uric acid, and so forth, are regarded as a result and not as a cause.

There is an extended consideration of blood pressure. Hypertension due to narrowing of the arterioles may be on an angiogenic basis (pressor substance) or neurogenic (stimulation of vasomotor centers). Dieckmann feels that the reaction from injection of pituitrin into patients with toxemia is an aid in distinguishing between preeclampsia and other hypertensive diseases. Patients with essential hypertension gave the most marked response to the cold pressor test. Urea clearance is considered as of little value in differential diagnosis. Dieckmann disregards the placenta or its changes as a cause of toxemia, and does not feel hormonal studies in toxemias have been carried on long enough to determine their significance. The high value of ophthalmic examinations is stressed. After evaluating the physicochemical changes in the pregnant woman he summarizes those regarded as of etiologic importance.

In the section describing the clinical aspects of the toxemias of pregnancy, hypertensive disease of pregnancy, and acute and chronic disease of the kidney are included. One finds a full discussion of renal ischemia, renin, and the mechanism of edema. The treatment of eclampsia includes a consideration not only of pharmacodynamics but a review of various treatments proposed by individuals or hospital. Very definite criteria are set for the termination of pregnancy. The final section of the book considers, statistically, the maternal mortality, the problems of the fetus in toxemic pregnancy. In considering the sequelae, Dieckmann does not believe that true eclampsia or pre-eclampsia results in permanent disease of the vascular or renal systems.

This volume is a splendid exposition of all phases of this most important problem in obstetrics, and the reviewer feels the objectives have been fully attained.

PHILIP F. WILLIAMS.

This manual on *Clinical Roentgenology of Pregnancy*⁵ is presented by Dr. Snow to illustrate the methods which he has been using successfully on his hospital services. There is a critical analysis and interpretation of various techniques, and Dr. Snow

⁴*The Toxemias of Pregnancy.* By William J. Dieckmann, Associate Professor of Obstetrics and Gynecology, University of Chicago, etc. 521 pages, with 50 text illustrations and three color plates. The C. V. Mosby Company, St. Louis, 1941.

⁵*Clinical Roentgenology of Pregnancy.* By William Snow, Director of Radiology, Bronx Hospital, Roentgenologist-in-Charge, Harlem Hospital, New York City. 178 pages with 117 illustrations. Charles C Thomas, Springfield, Illinois, 1942.

offers concisely the methods which he has found of greatest value. The technique is well illustrated, and the mathematics of the subject have been simplified as far as possible. There is a very timely discussion on the midpelvis, the importance of which has sometimes been overlooked in the anxiety regarding the amplitude of the inlet. The clinical problems of the fetus have been well handled. There is an excellent discussion regarding the soft-tissue technique and the localization of the placenta. Of particular value in this book is the well-illustrated series of case reports of unusual situations which Dr. Snow encountered. The illustrations are unusually clear. This manual should be of interest and of value to both the obstetrician and the roentgenologist.

PHILIP F. WILLIAMS.

In his *Contribution to the Study of Abdominal Pregnancy*,⁶ a brief thesis, Orta Menendez presents a well-balanced consideration of the subject with special emphasis on the diagnostic procedures to be followed when abdominal pregnancy is suspected. Most of his techniques are followed in this country although few would attempt to estimate the status of the uterine cavity by passing a very fine bougie (Douay-Broca maneuver). An extensive bibliography is appended.

R. J. WEISSMAN.

The minutiae of the essential features of the puerperal course of over 1,000 women, representing a great amount of careful work, were studied statistically by Ruelas in his thesis *Observations on the Clinical Course of the Puerperium*.⁷ Conclusions of interest include Ruelas' finding of more rapid involution and decreased incidence of afterpains in women of "hypergonadic biotype." The author recommends having the mother sit up in bed on the first post-partum day, up in a chair the second or third day, and ambulant by the fourth day. This procedure favors free drainage of lochia and normal bladder and bowel function. The literature is freely and extensively quoted.

R. J. WEISSMAN.

An interesting monograph, *Semiology of the Ovary*,⁸ presents Rodrigues' review of ovarian physiology, histology, and endocrinology. Most impressive are the excellent studies of vaginal smears (Shorr method), as a mirror of ovarian endocrine activity. Many of the plates are in color and full details of many staining techniques are given.

R. J. WEISSMAN.

The Second Edition of Louise Zabriskie's *Mother and Baby Care in Pictures*⁹ is one of the best examples of books for the pregnant woman and the mother of a newborn child, yet published. The text is characterized by brevity and clearness, every non-essential has been eliminated, and the text is medically correct. The outstanding feature of this book and one which makes it so extremely valuable is the profuseness of illustrations, of which there are 204. These illustrations are not only accompanied by full explanatory legends but correlate the text to an unusual degree.

⁶*Contribucion al Estudio del Embarazo Abdominal*. Por Dr. David Orta Menendez, Facultad de Medicina de la Universidad de la Habana. Tesis de Instructor, 1939.

⁷*Observaciones Sobre la Clinica del Puerperio*. Por Carlos Alexanderson Ruelas, Universidad Nacional Autonoma de Mexico, Facultad de Medicina. Editorial Cultura, Mexico, D. F., 1941.

⁸*Semiologia do Ovario, com um Estudo Particular da citologia Vaginal*. Par Dr. Francisco Victor Rodrigues, Professor de Clinica Ginecologica da Faculdade Fluminense de Medicina da Universidade do Brasil, etc. Casa do Livro Limitada, Rio de Janeiro, 1941.

⁹*Mother and Baby Care in Pictures*. By Louise Zabriskie, R.N., Director, Maternity Consultations Service, New York City, etc. Second edition, revised and reset. 208 pages with 204 illustrations, J. B. Lippincott Company, Philadelphia, 1941.

There are few steps in the development and early care of the baby from embryology up to the end of the first year, which are not illustrated. This book may be recommended heartily to all expectant mothers and their husbands.

PHILIP F. WILLIAMS.

Miscellaneous

This book, within its 276 pages, contains an epitome of the survey of human nature from the zoological viewpoint. *About Ourselves*¹⁰ is written by James G. Needham, professor emeritus of entomology and limnology. It is not remarkable for new ideas but for the cameolike presentation of a huge concept. Like a cameo, it is clear-cut, precise, delicate but vigorous. I read it from cover to cover with real enjoyment, pleased by the simplicity of its presentation and the large conception of its execution.

The author has traced our structure and development, and our first steps in learning, back to their sources in the animal world, starting with the automatic actions of lower forms, upward to the volitional control of the large brain of the primate.

Although viewed with the broad vision of the biologist, its pages overflow with human insight, kindness and humor, mellowed by age, but through the critical eyes of the entomologist. The main portions deal with man in his biologic aspects, which covers evolution, including the development of behavior, instinct, and learning. Then Part II deals with society in its biologic aspects, which embraces population, social nurture, and the components of social behavior. These components which include physiologic activities, instinct, folkways and reason, are taken up in detail. War, from its biologic aspects, covered from a similar point of view, and finally religion, are discussed. This book should appeal equally to the late adolescent and to the mature scientist.

R. T. FRANK.

Jason's monograph on *Hernia*¹¹ begins with an extensive historical outline in which the author attempts to give a complete nosography of this age-old common affliction. It appears that hernias were known and described as far back as existent archeologic documents can testify. With the zeal of a true historian, the author has collected numerous texts, antique and baroque, and frequently quotes and annotates them, sometimes showing a little impatience as to the slowness, cruelty, and fancifulness of the human mind in grappling with problems of bodily disorder. All this makes interesting and entertaining reading.

The main part of the book opens with a chapter devoted to statistics. Then follows a detailed description of the regional anatomy, and a discussion of the etiology of inguinal hernia, with numerous quotations from the writings of many authors. The references are all pertinent and some are fundamental and illustrate well the evolution of modern concepts of hernia pathology. However, here as in other parts of the book, the reader misses an occasional summarizing paragraph.

The treatment of hernia has recently been complicated by the revival of the injection methods. A full historical account of the subject and detailed technical steps are given, although the author himself probably has made use of this therapy in a limited fashion. The only type of hernia which he considers amenable to injection treatment is the indirect inguinal one. A chapter on trusses is likewise comprehensive and contains useful details.

Concerning the operative treatment, numerous procedures in vogue yesterday and today are described in detail and with a desire to make the historiography of hernia

¹⁰*About Ourselves*. By James G. Needham. 276 pages with illustrations by William D. Sargent. The Jaques Cattell Press, Lancaster, Pa., 1941.

¹¹*Hernia*. By Alfred H. Jason, Consulting surgeon, Long Beach Hospital, etc. 1325 pages with 355 illustrations. Blakiston Company, Philadelphia, 1941.

surgery as complete as possible. While it is most stimulating to read such full accounts of operative methods, the arrangement of the material makes quick orientation somewhat difficult. For instance, the full description of the Bassini operation, admittedly the keystone of modern hernia repair, is given much later than that of more complicated procedures and mere modifications. Nevertheless the author's discussion of the Bassini operation is excellent, and nowhere can one find a better and more succinct statement of the inherent difficulties of hernioplasty. The author's recommended technique for inguinal hernia varies according to the type. Emphasis is placed on the repair of the transversalis fascia wherever feasible.

Several excellent pictures of unusual varieties and odd contents of hernia sacs are found in the chapter on femoral hernia. The advantages of the inguinal approach for this type of hernia, on account of the better orientation and the greater accuracy in dealing with compromised intestines, are emphasized. Among a total of 1,000 cases of hernia coming under the observation of the author, femoral hernia was encountered in 17 male and 49 female patients. At the same time, inguinal hernia in female patients was still three times more frequent than the femoral type, while in men the ratio was as high as 20:1.

Special chapters are devoted to umbilical, median line, incisional, diaphragmatic, pelvic, sciatic, obturator, and intra-abdominal hernias with descriptions of operative procedures for these, sometimes rare, findings.

In a concluding chapter on recurrent hernia several practical questions are touched upon. Wound infection after repair of an inguinal hernia is not necessarily followed by recurrence. As a matter of fact, in the author's experience, they have been rather the exception. In infants, children, and young adults hernioplasty is unnecessary or harmful because the suture of a well-functioning internal oblique muscle leads to its degeneration. The technique for extensive direct hernia, as advocated by the author, is depicted in this chapter in one drawing. Simultaneous bilateral operations are considered more conducive to postoperative complications and to reduction of permanent results. The author prefers spinal anesthesia and does not seem to belong to the advocates of the silk suture technique.

The third section of the book is devoted to the so-called "compensable hernia," an issue brought before courts and compensation boards innumerable times. Besides a lucid exposition of the etiologic factors which enter into the making of hernia, a comprehensive survey is given of legal procedures and decisions handed down by courts from Alaska to the Straits of Magellan.

The book contains over 350 illustrations, the majority from the very attractive and instructive sketches made by Alfred Feinberg. Literature references, not always complete, are inserted in the text. No separate bibliography is given in tabulation form or as footnotes. The size of the book will limit the extent of its use, but it does contain practically everything about hernia. Perhaps condensation of historical and other material, with rearrangement and more emphasis on the salient and the pertinent, may greatly enhance its handiness.

G. E. GRUENFELD.

*The Doctors Mayo*¹² by Clapesattle proved most enjoyable reading and should prove so to all medical men who have any interest in the history of the development of American medicine from 1845 on. It deals with two generations of the Mayo family, starting with William W. Mayo, born in England in 1820, who emigrated to the United States in 1845. For a short time he was a pharmacist in the old notorious Bellevue Hospital in New York. By gradual stages during which he practiced all

¹²*The Doctors Mayo.* By Helen B. Clapesattle. Illustrated. The University of Minnesota Press, Minneapolis, 1941.

sorts of professions, including a fancy tailoring establishment in Lafayette, Indiana, he came to Minnesota in 1854. During these years he supplemented his fragmentary medical knowledge by working under Dr. Deming and likewise attending the proprietary medical school of La Porte, Indiana. In Minnesota his activities included exploration of Lake Superior region, farming, veterinarian practice, justice of the peace and ferryman. By 1861 he had established a real medical practice in the region of Le Sueur which was interrupted by a serious outbreak of the Sioux Indians. The senior Mayo finally moved to Rochester in 1864. William J. Mayo was born in 1861 and Charles Mayo in 1864.

The elder Mayo evidently was a wide-awake, community-minded individual who did not shy from work of any kind and who continued to improve his medical knowledge throughout the years. He was the first man to practice ovariectomy in Minnesota, establishing an increasing reputation as a skillful surgeon. His sons, William and Charles, were early initiated into the mysteries of medicine, received as good an education as was possible locally, and eventually graduated as physicians. They started by helping their father who, as well as the sons, made pilgrimages to various medical centers to improve their knowledge which almost always showed some advance over the current medical understanding throughout the country. The gradual increase of their practice and the requirements of the community encouraged the Sisters of St. Francis to start a modest hospital at Rochester from which the present world-famous Mayo Clinic developed. From this modest beginning a slow but progressive growth can be noted. The book shows convincingly how hard work, attention to detail, widespread acquaintanceship, the interest of the community and especially of its newspapers, the constant enlargement of medical acquaintanceship and friendship, blossomed and came to fruition in the present organization which likewise was not planned but developed by evolution.

The rapid growth of the Mayo Clinic was bound to produce jealousies, antagonism, and active hostility, particularly in the neighboring large cities. This resulted in many accusations of unfair practice, of unethical advertising, etc. All of these phases are discussed freely and on the whole impartially. After the death of the senior doctor, and after the two brothers, William and Charles, had reached full maturity, they gave a liberal endowment for the continuation of the Clinic to the University of Minnesota of which it is now a part.

Reading of this volume will be of great interest to the older physicians because they will encounter so many friends and former teachers within its pages. In addition, it gives a most illuminating picture of the growth of American medicine throughout the country. The younger men will profit much by its perusal and will see by what slow and painful stages modern medicine has been born. How great an appeal the book will have for the laity is hard for the reviewer to judge.

The sole discordant notes appearing in this well-written volume, arise from the apparent hesitation shown in writing this volume. There can be no question but that all three Mayos are well worthy of such a careful biography. It is to be regretted that none of them were willing to write an autobiographic report. If some readers who are not in sympathy with group practice and certain evils which have developed therefrom, feel that the treatment accorded by the author to her subjects is too lenient or favorable, this after all, is the common fault of biographers in general.

R. T. FRANK.

Within the past ten years changes in concepts concerning and advances in specific therapy of communicable diseases have been extensive and in some cases bewildering, and therefore there is value in a book which attempts to present what is both old and new and which also sorts the wheat from the chaff. Not

only does **Clinical Immunology, Biotherapy and Chemotherapy**¹³ by Kolmer and Tuft cover the diseases caused by bacteria, viruses, and fungi, but it includes discussion of those immunologic processes which are strange and potentially harmful, namely the allergies.

A little more than one-third of the subject matter is devoted to outlining fundamentals concerning the agents of disease and their action, and the basic knowledge relating to immune reactions and the immune antibodies. In this first part, in concise fashion, an excellent presentation of this field is given, so that little that is pertinent to an understanding of infection and specific therapy is omitted.

The second part takes up separately the specific diseases. All forms and aspects of therapy are presented. Prophylactic and curative measures are considered and in many cases a variety of measures are discussed. The material in these chapters is well organized and in addition summaries of the most important points are given at the end of each chapter.

In view of the effort which has been made to place within these pages the complete knowledge of biotherapy and chemotherapy as applied to specific diseases, this volume serves a valuable purpose for reference and consultation.

MOYER FLEISHER.

The importance and constantly increasing use of blood transfusions should make this book, **The Blood Bank and the Technique and Therapeutics of Transfusions**,¹⁴ by Kilduffe and DeBakey, especially timely.

Following a short discussion of the history of transfusion, the authors present an important chapter on the fundamental physiology upon which blood transfusions depend. The indications and recommendations for the use of this measure in hemorrhage and shock and other conditions are described. Following a short discussion of the military aspects of transfusion and the special types of transfusion, the text is largely devoted to the technique surrounding this method, in all its phases. Four chapters are given to a discussion of the blood bank, the technique essential in its institution, the method of operation, and the physical and biochemical changes which may occur in stored blood.

The subject of plasma transfusion follows the same method of presentation. Of more direct importance to the clinician should be the final chapters of the book which describe the methods and technique of transfusion under various circumstances. The final chapter discusses the most frequent complications of blood transfusions and stresses the potential dangers of this often life-saving procedure.

The book is extensively illustrated and the review of the literature is tremendous, one chapter having 650 references. It would seem that such a book as this would be a necessary working manual for the blood transfusion department of all hospitals and clinics.

PHILIP F. WILLIAMS.

A Primer on the Prevention of Deformity in Childhood¹⁵ has been prepared by Dr. Richard Beverly Raney in collaboration with Dr. Alfred Rives Shands, Jr. It

¹³**Clinical Immunology, Biotherapy and Chemotherapy.** By John A. Kolmer, Professor of Medicine, Temple University School of Medicine, etc., and Louis Tuft, Assistant Professor of Medicine, Temple University School of Medicine, etc. 941 pages, illustrated. W. B. Saunders Company, Philadelphia, 1941.

¹⁴**The Blood Bank and the Technique and Therapeutics of Transfusions.** By Robert A. Kilduffe, Director, Laboratories, Atlantic City Hospital, etc., and Michael DeBakey, Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana, etc. 558 pages with 214 illustrations and one color plate. The C. V. Mosby Company, St. Louis, 1942.

¹⁵**A Primer on the Prevention of Deformity in Childhood.** By Richard Beverly Raney, Associate in Orthopaedic Surgery, Duke University School of Medicine, etc. In collaboration with Alfred Rives Shands, Jr., Medical Director, Alfred I. du Pont Institute of the Nemours Foundation, etc. Illustrated by Jack Wilson. 188 pages with 88 figures. National Society for Crippled Children in the U. S. of America. Elmyra, Ohio, 1941.

is distributed by the National Society for Crippled Children at the nominal price of one dollar.

Since the effectiveness of efforts in the prevention of deformities obviously depends upon their prompt application, this volume was written specifically for those who most likely will be the first to see the afflicted child, namely family physician, welfare worker, and health nurse. In accord with this aim the primer is written in plain, simple language avoiding, as far as possible, technical terms. It gives in detail the characteristics, causes, and methods of prevention and treatment of all the more common congenital and acquired conditions prone to result in permanent deformity.

The obstetrician often is one of the first to see such anomalies, whether congenital or unfortunately acquired incident to birth. He cannot fail to appreciate such a ready reference book to inform him of the best procedures to be applied promptly. The value of this little book is greatly enhanced by 88 instructive text illustrations, 37 of them taken from Shands' well known *Handbook of Orthopaedic Surgery*. (The C. V. Mosby Co., 1940.)

HUGO EHRENFEST.

The two fields in which radiation therapy has been proved to be effective and about which much has been published are cancer and dermatology. The *Roentgen Treatment of Infections*¹⁶ by Kelly and Dowell is a text intended to fill the gap which exists in a third great field in which x-ray therapy is effective.

The introductory part of the text deals with x-ray physics and the fundamentals of radiation therapy. This is presented simply and directly and is supplemented by an adequate bibliography. After a review of the background and general considerations of roentgen therapy in infections, the authors undertake an exhaustive discussion of gas bacillus infection. They present their evidence to prove the efficacy of x-ray therapy in gas gangrene, a method of treatment which if used early will, they claim, cut the mortality rate to about 10 per cent. They conclude that, "only the exceptional patient dies of gas bacillus infection alone if treated with x-rays according to directions." In view of the considerable controversy which exists at the present time in the literature dealing with this subject and the lack of controlled clinical investigations, or proved laboratory experimentation, it would seem that the authors have adopted an extreme point of view, which, at the present time, seems open to question. No harm whatsoever can be produced by x-ray therapy for gas gangrene, provided it is used under experienced supervision, and it is hoped that in the present world conflict, the opportunities for its use will be utilized to the utmost with a view to establishing to the satisfaction of all, the specific value of this modality. Radiologists will question the wisdom of the suggestion that because only low voltage x-ray apparatus is used and small dosages of x-ray applied, therefore, the average physician can undertake this type of therapy. A superficial knowledge of x-ray principles does not qualify one for superficial x-ray therapy.

Because of the authors' unusual interest in the treatment of gas gangrene, peritonitis, and pneumonia with x-ray, a disproportionately large part of the book is devoted to these subjects, more than 80 per cent, with the result that there is a tendency to direct emphasis away from the more common, albeit less dramatic and fatal, inflammatory conditions for which radiation therapy can be of value. To the obstetrician and gynecologist, the chapters dealing with parotitis, peritonitis, and acute abdominal conditions will be of particular interest and value.

¹⁶*Roentgen Treatment of Infections*. By James F. Kelly, Professor and Director of the Department of Radiology, Creighton University School of Medicine, etc., with collaboration of D. Arnold Dowell, Assistant Professor of Radiology, Creighton University School of Medicine, etc. 432 pages with 122 illustrations and charts. The Year Book Publishers, Inc., Chicago, 1942.

The authors have permitted their enthusiasm and keen interest in the subject of gas gangrene and its treatment by x-ray to overemphasize some of the material in the text resulting in too great detail and, at times, repetition. For the average physician and surgeon, the material could have been handled more effectively and directly in a smaller, brief monograph.

H. R. SENTURIA.

In *The Microbe's Challenge*,¹⁷ Dr. Eberson has described for the always interested lay public the life history and biologic characteristics of a number of our most potent enemies. This is a fine story of the development of preventive medicine and portrays fundamental advances and principles of microbiology. The outstanding discoveries of Pasteur, Koch, Jenner, and other great men in preventive medicine are described so clearly and interestingly that the text should be of just as much interest to the medical profession as to the laity, for whom the book is intended. This succinct presentation of the major epidemic diseases and the manner in which present-day medicine is fighting such conditions, reflexly should lead to widespread support of present methods in research to eliminate challenges to national and international public health. The book is commended as accurate and informative reading for the lay public.

PHILIP F. WILLIAMS.

Dr. Kahn presents the second edition of his treatise entitled, *Our Sex Life*.¹⁸ While the book is devoted to the problems of sexual relationships, the author has included problems of fertility and infertility. Proceeding to the neuropsychic aspects of sex life, he discusses those situations which are often functional or neurologic in origin. He then presents the diseases of sex life, their complications, and social aspects. There is a section on the nature of prostitution in which the social and legal phases are discussed.

The author returns to sex education in discussing the juvenile sex life and explains the duties of both parents and individual and communal sex education programs. The problems which occur with unmarried people are handled without moralizing. The author offers a sane discussion on the difficult problem of extramarital sexual intercourse. This volume concludes with a well-thought-out chapter on solutions of the sex problem. There are a few medical mis-statements in this book regarding the life-cycle of spermatozoa, the fertile period, and the treatment of nausea and vomiting.

There are few problems concerning sex life which one cannot find in this book and for counsellors on such a topic the comprehensive treatment of the subject may be of value.

PHILIP F. WILLIAMS.

¹⁷*The Microbe's Challenge*. By Frederick Eberson, Ph.D., M.D., Director of Laboratories, Gallinger Hospital, Washington, D. C. 354 pages. The Jaques Cattell Press, Lancaster, Pa., 1941.

¹⁸*Our Sex Life*. A Guide and Counsellor for Everyone. By Fritz Kahn. Second, revised edition. 459 pages. Illustrated. Alfred A. Knopf, New York, 1942.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 21, 1941

The following papers were read:

Wound Disruption and Its Management. Herbert E. Schmitz and Dr. James H. Beaton, Grand Rapids, Michigan (by invitation). (For original article, see page 806.)

The Use of Ergonovine in the Placental Stage of Labor. Dr. M. Edward Davis and Dr. Melbourne W. Boynton (by invitation). (For original article, see page 775.)

MEETING OF DECEMBER 19, 1941

The following symposium on Hysterectomy was presented:

Vaginal Hysterectomy. Dr. Harry Boysen (by invitation).

Subtotal Hysterectomy. Dr. Lester E. Frankenthal, Jr.

Total Hysterectomy. Dr. Eugene A. Edwards.

Summary. Dr. George H. Gardner.

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF NOVEMBER 6, 1941

The following papers were presented:

Spontaneous, Painless Parturition in a Case of Pregnancy Complicated by Transverse Myelitis. By Dr. J. Stanley Cohen (by invitation). (For original article, see page 873.)

The Management of Dead Abdominal Pregnancy. By Dr. J. P. Quindlen and Dr. R. C. McElroy (by invitation).

Evaluation of the Metranoikter in Dysmenorrhea. By Dr. S. Leon Israel.

Cotton Suture in Gynecology. By Dr. Saul P. Savitz.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Labor

Nakadima, T.: Statistical Study of Elderly Primiparas, *Jap. J. Obst. & Gynec.* 24: 33, 1941.

The author analyzed the records of 109 primiparas over thirty years of age. In this group he noted the difference between late marriage and lapse of a number of years after marriage before pregnancy took place. Toxemias, long duration of labor, premature rupture of the membranes, weak uterine pains and perineal lacerations were more common than usually. Because of these facts, the author favors cesarean section in cases of breech presentation in an elderly primipara.

J. P. GREENHILL.

Hemmingway, Ruth V., and Chung-Teh, Chou: Report of 729 Obstetrical Cases in Chungking, *Chinese M. J.* 59: 90, 1941.

Pelvic measurements on women from 16 provinces of China, 710 measurements in all, tend to confirm the observation that the average for China is lower than that for some other countries.

The average blood pressure for the group was systolic 120 and diastolic 80.

A table of the first menstrual periods of 434 women shows that on an average it first appears at the age of 15.2 years (Chinese count).

A study of the complications encountered in this group shows 1 per cent for eclampsia and 1 per cent for placenta previa. Rupture of the uterus occurred in 0.2 per cent, and abruptio placentae in 0.4 per cent.

Of 729 deliveries, 82 per cent were spontaneous, 8.6 per cent were forceps deliveries, and 2.4 per cent were podalic extractions. Three per cent had cesarean sections. Craniotomy was required in 1 per cent and version in 3 per cent.

Head measurements, made on a small number, suggest that heads of Chinese babies do not differ in measurement from those reported in the United States, in spite of the difference in the measurements of their mothers' pelvis.

C. O. MALAND.

Cantone, Carlo: Premature Delivery in the Department of Obstetrics and Gynecology of Dr. Vercelli, *Folia demograph-gynec.* 37: 117, 1940.

The author reviews the literature and considers the many angles of the problem of premature labor. He stresses certain differences in the statistics obtained by himself and those offered by other writers. He confirms the importance of regional and constitutional factors in premature labor. He finally suggests that the working classes, especially the farm women, should desist from their arduous duties during

the latter part of pregnancy in order that the incidence of premature labors and the rate of consequent prenatal deaths be lowered.

MARIO A. CASTALLO.

Kirchner, W.: *Twilight Sleep With Dilaudid and Pernocton*, Zentralbl. f. Gynäk. 64: 1424, 1940.

The author administers 0.002 Gm. of dilaudid intramuscularly when the patient is definitely in labor. At least three hours later 4.5 c.c. of pernocton is slowly administered intravenously. If it is apparent, however, that delivery will be complete within an hour or less, the pernocton is not given. Although some of the infants have an asphyxiated appearance at birth, in the author's series they all cried strongly and none were lost. Amnesia and analgesia for the labor are highly satisfactory.

R. J. WEISSMAN.

Robertson, Kenneth M.: *Intravenous Anesthesia in Obstetrics*, Brit. M. J. 1: 815, 1941.

The author recommends intravenous barbiturate anesthesia in obstetrics, increasing thereby the patient's comfort, eliminating the unpleasantness and inconvenience of open ether or chloroform, and relieving the assistants to perform duties other than anesthesia. Intravenous evipan was used during the second stage of labor in over fifty cases including low forceps delivery, breech extraction, and manual rotation with forceps extractions of persistent occipitoposterior positions. One gram of evipan in a 10 per cent solution was used in each case, giving a very complete anesthesia, particularly with earlier premedication as chloral and broximide or morphine. One or two patients with no premedication showed some movements of the legs during delivery. The third stage in each case was uneventful. There were no complications in the progress of mother or child. The patient usually recovered consciousness shortly after delivery.

Smaller dosages were used in 7 cases of spontaneous deliveries with cephalic presentation. One of these infants had some delay in respiration.

Evipan was also used with success in perineorrhaphies.

FRED L. ADAIR AND WM. ROSENBAUM.

Fuchs, H.: *A New Obstetrical Phenomenon: Wry Neck*, Zentralbl. f. Gynäk. 65: 619, 1941.

The author reviews the literature on 180° rotation of the head during labor. The condition may be diagnosed by finding on vaginal examination the anterior fontanel to be on the same side as the infant's back as felt by abdominal palpation. Radiographs confirm the finding. The author supports his case with a photograph, showing the infant tolerating 180° rotation with no apparent discomfort. This condition is seemingly innocuous for the life of the infant and may be caused by either rotation of the body on the head during labor contractions or by active rotation of the head on the body.

R. J. WEISSMAN.

Perez, M. L., and Rosenwasser, J.: *Neurovegetative System and Uterine Dynamics in Labor*, Bol. Soc. chilena de obst. y ginec. 5: 95, 1940.

The authors present, with detailed protocols of 60 cases, their conclusions as to the relation of type of uterine contractions to the status of the patient's vegetative nervous system. Physiologic uterine contractions are in direct relation with good sympathetic excitability. Uterine hypodynamia is found in cases having vagal or

sympathetic hypotonus. In vagotonic individuals the contractions are of a spasmodic irregular nature. The authors feel that prior determination of an abnormal neuro-vegetative status permits a rational therapy at term to bring it into a balance favorable for good uterine contractions.

R. J. WEISSMAN.

Schultze, G. K. F.: *The Functional Independence of Each Half of the Uterus*, Zentralbl. f. Gynäk. 65: 2, 1941.

The author presents the evidence of serial radiography of the uterine cavity as outlined by contrast medium to show that each lateral half of the uterus contracts independently of the other. This might have been expected from the duplex embryologic development of the uteri. Its clinical significance is yet to be established, but Schultze feels that it attains importance in a possible explanation of some cases of abortion in which the effect of unilateral uterine contraction may be dislodgment of the implanted ovum. He would like to add this independent contractility as a possible cause of dystocia and thinks it should be considered in prolonged ineffective labor pains where other causes of dystocia cannot be found.

R. J. WEISSMAN.

Lüttge, W.: *Full Baths at Term*, Zentralbl. f. Gynäk. 65: 844, 1941.

The author reviews the opinions to be found in the literature on the dangers of a full tub bath at term, especially with regard to the danger of ascending infection after rupture of membranes, to all of which he takes exception. Lüttge favors the full bath with green soap and a chlorine antiseptic added to the water. Where only 5 to 10 liters of water are consumed in a sponge or shower bath, the tub bath affords a great dilution of bacteria with 200 to 300 liters of water. A decrease in puerperal morbidity was ascertained in patients having a forceps delivery after full bath, and the author considers the bath the best predelivery antiseptic. This conclusion is based on results with 12,000 patients with intact membranes and 3,000 patients with ruptured membranes. The psychic influence of the bath is favorable. The bath often stimulates or initiates labor pains. Premature rupture of membranes may be diagnosed by prompt onset of labor with the bath, quinine, and hot applications, and the diagnosis of postmaturity may be excluded if labor starts. Primiparous labor is shortened to ten hours in many cases and to six hours for multiparas.

R. J. WEISSMAN.

Doneddu, F. P.: *The Determinative Cause of Labor*, Ginecologia 16 (Series 2): 483, 1940.

The author reviews the multiple theories regarding the determinative cause of labor. He covers theories and hypotheses advanced from the Hippocratic epoch to the era of endocrinology. He adds nothing original and is in agreement with prevailing views on endocrine factors.

The material is well arranged. It is presented in a concise and chronologic manner. The article may be of particular value to those who seek continental sources for historical data upon this subject.

CLAIR E. FOLSOME.

O'Sullivan, J. V.: *Severe Uterine Inertia Treated by Cutting the Cervix*, Brit. M. J. 2: 852, 1939.

A method of expediting cases of severe uterine inertia is described. This consists of cutting the cervix at 3 and 9 o'clock of the clock dial, the incisions extending in-

ward not more than half an inch from the edge of the cervix. The author advises that the procedure be preceded and followed by a hot antiseptic douche. After being cut, the cervix is "pushed gently up over the front of the head."

Fourteen cases are discussed, with good results in all cases with the exception of one in which the mother developed septicemia and peritonitis and died twelve days after delivery.

F. L. ADAIR AND E. CHEYDLEUR.

Louros, N., and Kyriakis, L.: *Artificial Initiation of Labor—Use of Stilbestrol and Progynon*, Zentralbl. f. Gynäk. 64: 957, 1940.

Although in a series of 2,000 cases, weak labor pains as a rule were successfully treated by the use of quinine, heat, and thymophysin, some were found to be absolutely unaffected. It is the opinion of the authors that the initiating mechanism of labor for the most part consists of a sudden flooding of the organism with follicular hormone, sensitizing the myometrium to the influence of posterior pituitary hormone.

Using Cyren (the dipropionic acid ester of dioxydiethylstilbene) Louros and Kyriakis gave 2.5 mg. (equivalent to 5 mg. estradiol) intramuscularly in hourly doses to a total of 10 to 12 mg. in 38 cases in an effort to initiate labor. There was no result in 32 cases, but light uterine contractions in 6 cases. Combining the same dosage of cyren with 200,000 I.U. of progynon, only a few cases showed uterine contractions. In 32 patients who had reached or passed term, the authors followed the above treatment with quinine and thymophysin. Labor began in an astonishingly short time, and 24 primiparas reached the second stage in an average of twelve hours, 8 multiparas in seven and one-half hours, and 9 elderly primiparas in fourteen and one-half hours. No untoward effect was noted on mother or child, and there was no inhibition of lactation.

R. J. WEISSMAN.

Effkemann, G.: *Oxytocic Effect of Follicle Hormone*, Zentralbl. f. Gynäk. 65: 338, 1941.

The author administered 10 mg. of estradiol by vein to a group of 27 patients at term. Labor began in all patients within eighteen hours, proceeding to delivery. The mechanism of the estradiol effect is discussed, and Effkemann concludes that when administered by vein the hormone exerts not a sensitizing, but an acute and direct effect on the myometrium.

R. J. WEISSMAN.

Friedrich, H.: *Clinical Study of Follicle Hormone Initiation of Labor*, Zentralbl. f. Gynäk. 65: 613, 1941.

Excluding cases of primary or secondary atony of the uterus, the author administered to a group of women radiographically proved to be past term without labor, large doses of progynon in combination with a small dose of castor oil. If labor was not induced, quinine-thymophysin induction was attempted some hours later. A similar group having the above medication without follicle hormone went into labor on an average three hours sooner. Results in the case of premature rupture of membranes in otherwise normal patients without labor were more promising, as administration of follicle hormone appeared to bring on active labor in a series of 87 cases in an average of 3.7 hours. Contrary to expectation there was no noticeable inhibiting effect on subsequent lactation.

R. J. WEISSMAN.

Gross, Rudolf: The Occurrence, Significance and Treatment of Premature Rupture of the Membranes, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 163, 1940.

One thousand consecutive obstetric cases were used to study cases of premature rupture of the membranes. By arbitrary definition, premature rupture of the membranes includes all cases in which rupture occurred before the cervix had become half dilated. On this basis, 31 per cent of labors were associated with premature rupture of the membranes, with primiparas showing a little more and multiparas somewhat less than the average incidence. No very significant relationship could be demonstrated between this condition and pelvic contraction, anomalies of position or presentation or size of the child. Multiple pregnancy showed an increased incidence. When premature rupture occurred, labor was shortened but no deleterious effect on mother or child was demonstrable. No therapy is, then, indicated.

J. L. McKELVEY.

Metz, Alfons: The Effect of Premature Rupture of the Membranes on Duration of Labor, *Ztschr. f. Geburtsh. u. Gynäk.* 121: 199, 1940.

The same thousand cases described by Gross were analyzed further. When rupture of the membranes occurred (spontaneously, presumably) before labor, the latent period averaged eleven to twelve hours with an average first stage of nine hours for the primipara and five hours for the multipara. First stage was thus shorter than average. No effect on the second stage was demonstrated. It seemed that the longer the latent period, the shorter the first stage and vice versa.

J. L. McKELVEY.

Short, C. R.: Induction of Labor by High Puncture of the Membranes, *Bristol Med.-Chir. J.* 57: 121, 1940.

The author induced labor by high puncture of membranes and withdrawal of 16 to 20 ounces of fluid in 87 cases, 47 of which were primiparas. Toxemia, eclampsia, dystocia, toxemia with twins, hemorrhage, postmaturity, pyelitis, mitral stenosis, insanity, and epilepsy were the indications in this group. Labor was induced from the thirty-sixth week of pregnancy onwards. Due to maternal apprehension a general anesthetic was given for the procedure in 14 cases. Ordinarily hyoscine and morphine are given one hour beforehand. The vagina and cervix are cleaned, and without grasping the cervix, it is gently dilated with one finger and the special cannula-catheter is passed up between the membranes and the uterus to a point above the fetal head where puncture is made. In general, labor began in twenty-four hours. The average duration of labor was fifteen hours for primiparas and eight for multiparas, shorter than in the average normal case at term. The author explains 6 stillbirths in this series as being due to factors other than induction, such as the use of forceps, quinine and pitocin and other unusual measures. The corrected morbidity as measured by pyrexia was 2.3 per cent, although the temperature in the two cases involved did not rise above 100.4° F. Shorter labor and salvage of more mothers and infants are the author's justifications for a wider use of high puncture of the fetal membranes.

R. J. WEISSMAN.

Gairdner, Alan, Hadley, Margaret, and Jackson, L. N.: A Hundred Cases of Breech Presentation, *Lancet* 1: 273, 1941.

Of 100 consecutive cases of breech presentation in hospital and private practice, 11 were treated successfully by version and delivered as vertices; 26 were delivered by cesarean section, and 63 by the vagina. There was no maternal mortality

but the total of stillbirths and neonatal deaths was 19, only one (a monster) being among the infants delivered by cesarean section. Twenty-seven of 53 breech deliveries in the hospital series were by cesarean section while none of the 36 breech deliveries in the private practice series was by section. Ten of the infant deaths were in the first series and 9 in the second.

The authors state that if version fails, cesarean section is the treatment of choice, especially in primiparas or where some degree of pelvic contraction is diagnosed. Breech vaginal delivery is less risky to the child in multiparas than in primiparas.

CARL P. HUBER.

Brunner, C.: Attempt to Hasten the Placental Stage and Diminish the Loss of Blood, *Monatschr. f. Geburtsh. u. Gynäk.* 111: 249, 1940.

The author modified the method of Mojon and Gabaston for hastening separation of the placenta. Immediately after ligating the umbilical cord, the injection into the umbilical vein was started if there was evidence of "uniform adherence of the placenta." At first the fluid injected consisted of a sodium chloride solution with calcium, adrenalin, anterior pituitary, and gynergen. Because this did not produce the desired results, the solution was changed to a concentrated sodium chloride solution (20 to 30 per cent) with glucose (30 to 40 per cent) similar to the solution used for obliterating varicose veins. In a series of 500 cases, the results obtained by this procedure are encouraging. Thus, in the group where this method was used, the incidence of atony of the uterus was 3.8 per cent, whereas in the control group it was 11.8 per cent. Likewise, in the injection group, the uterus had to be explored for placental remains in 0.8 per cent, whereas in the control group this was necessary in 3 per cent of the cases. Manual removal of the placenta was resorted to with equal frequency in both groups.

J. P. GREENHILL.

Farquhar, Murray: Causes of Post-Partum Haemorrhage, *Brit. M. J.* 2: 1180, 1939.

Uterine massage following delivery is probably unnecessary although it is the "general rule" in England.

If a patient lies for a long time on her side before the placenta comes away the uterus tends to fall up into the abdomen and a disturbance of the neuromuscular mechanism is produced which causes bleeding.

If several attempts at placental expression result only in the expression of large clots, manual removal should be done while the patient's condition is still good.

Some cases of profuse hemorrhage following the third stage may be due to the presence of unusually large arterial trunks close to the placental site.

The author prefers never to pack a uterus but to use bimanual compression followed by a hot douche.

F. L. ADAIR AND E. CHEYDLEUR.

Hoff, F., and Spannagel, T.: Post-partum Ice-Bag Prophylaxis, *Zentralbl. f. Gynäk.* 64: 945, 1940.

The authors' method of hastening the third stage of labor and diminishing the usual blood loss is to place a heavy (1,200 Gm.) ice bag over the uterine area immediately after the delivery of the child. Two series of 2,000 cases each, comprising material from the Heidelberg Clinic, were compared in regard to the weight of blood lost post partum, one group receiving the so-called ice-bag prophylaxis.

The crude figures show a hemorrhage of over 1,000 Gm. in 0.55 per cent of ice-bag cases as against 2.6 per cent in cases without this prophylaxis. Similar differences appeared in other groups in which bleeding was less. When the two series were broken down into groups with and without lacerations, spontaneous and operative deliveries, a like result appeared in favor of the use of the ice bag. The duration of the third stage in 0.25 per cent of ice-bag cases was over one hundred and twenty minutes as against 0.65 per cent without ice bags.

Comparing various procedures carried out in the immediate post-partum period, the most common was the Credé expression of the placenta with and without narcosis in 12 cases followed by application of ice bags and 45 in which these were not used. Puerperal complications were found in 373 of the untreated cases and 254 in which cold was applied.

R. J. WEISSMAN.

Hoffstrom, K. A.: A Series of More Than 1,000 Forceps Deliveries, *Monatschr. f. Geburtsh. u. Gynäk.* 112: 12, 1941.

The author reports a series of 1,047 forceps deliveries performed during the last thirty years at the Tammesfors Clinic. This is an incidence of 4.6 per cent for forceps deliveries. There were 502 outlet forceps, 329 midforceps, and 219 high forceps operations. The corrected fetal mortality in these groups was 2.1, 4.1, and 8.5 per cent, respectively. The author emphasizes that experience has shown the importance of replacing high forceps operations by cesarean section, particularly in cases where there is cephalopelvic disproportion. He is opposed, however, to the widespread use of cesarean section without thorough examinations.

J. P. GREENHILL.

Dietrich, H. A.: Forceps on Aftercoming Head, *Zentralbl. f. Gynäk.* 65: 526, 1941.

The author reviewed 17,070 deliveries from 1927 to 1937. The incidence of primary breech presentation was 4.7 per cent. An additional 111 cases were converted to breech for extraction. Twenty cases were sectioned and 906 were delivered with the aftercoming head, of which 40 per cent delivered spontaneously, leaving 556 who required manual or forceps assistance. Of 325 infants delivered with manual assistance, 18 per cent were either stillborn or died in their first ten days. Of 231 having forceps applied to the head, 9 per cent were stillborn or died in the first ten days. Dietrich emphasizes the increased safety for the child with the application of the forceps and discusses in detail the application in various positions of the head.

R. J. WEISSMAN.

Bock, A.: Separation of Symphysis in Spontaneous Delivery, *Zentralbl. f. Gynäk.* 65: 494, 1941.

Bock reviews the statistics on symphyseal separation and notes in the study of latest world literature an increase in the percentage of separations in spontaneous delivery from 17 to 65 per cent. This is a relative increase and is due in large part to the decrease in high forceps operations as well as a general decrease in the proportion of operative deliveries from below as result of the improvement in radiographic diagnosis and cesarean section. Radiography is important in this condition more to differentiate between loosening and rupture of the joint than merely to make a diagnosis of symphyseal traumatization since the symptoms of rupture are characteristic, but there are cases in which roentgenologically there is definite separation

without clinical symptoms. Two cases of separation in primiparas are cited by Bock. In one case symptoms appeared immediately after delivery, and in the other after twenty-four hours. Both were cured by application of a broad pelvic swathe. The author has no explanation for these accidents. The first patient was of a gracile type, but her baby weighed only 3,500 Gm.; the second had a 4,250 Gm. infant but her pelvis was entirely adequate. The author feels all such cases should be reported, if only for their medicolegal significance. The physician involved in litigation, when this accident has occurred in association with forceps delivery, is justified in asserting that symphyseal separation can and does occur with spontaneous birth.

R. J. WEISSMAN.

Häutsch, L.: Symptomless Course of Uterine Rupture Due to Incarceration of Placenta in Cesarean Scar, *Zentralbl. f. Gynäk.* 64: 1818, 1940.

A 29-year-old gravida v had a cesarean section delivery of her fourth child 3 years previously. A week before hospitalization she experienced severe abdominal pains while doing her housework. Her physician noticed nothing abnormal on examination, except a yellowish vaginal discharge, and as the pain subsided the patient continued her work. Two days before hospitalization severe pain again recurred and continued. After a prolonged labor, a dead infant was delivered, and the patient seemed in good condition except for slight motor restlessness and heavy breathing. The placenta, however, was not forthcoming, and fifteen minutes later the patient went into collapse and died within half an hour. At autopsy almost 2 liters of free blood were found in the abdomen. A large clot filled the left iliac fossa. The genital tract was removed in toto and at the site of the old uterine scar, where the wall had thinned to almost 1 mm., there was a perforation several centimeters in diameter, through which protruded placental tissue. The placenta had been implanted over the site of the scar. The author concludes that the rupture took place two days before admission, when the patient for the second time had experienced pain and dizziness. The placenta had apparently successfully plugged the tear until actual labor set in.

R. J. WEISSMAN.

Gauss, C. J.: A New Craniotomy Instrument: The Würzburg Basiotriector, *Zentralbl. f. Gynäk.* 65: 624, 1941.

The author describes in detail a new basiotriector whose essential new feature seems to be in the fenestrated outer blades which are open like those of a Piper forceps. The distal curve, however, is almost flattened, giving the advantages of a larger grasp on the fetal head without the possibility of engaging tissues on the infant's lower neck and shoulders.

R. J. WEISSMAN.

Dr. Joseph Bolivar DeLee died at his home in Chicago, April 2, 1942. An extended obituary will appear in the June issue of the JOURNAL.

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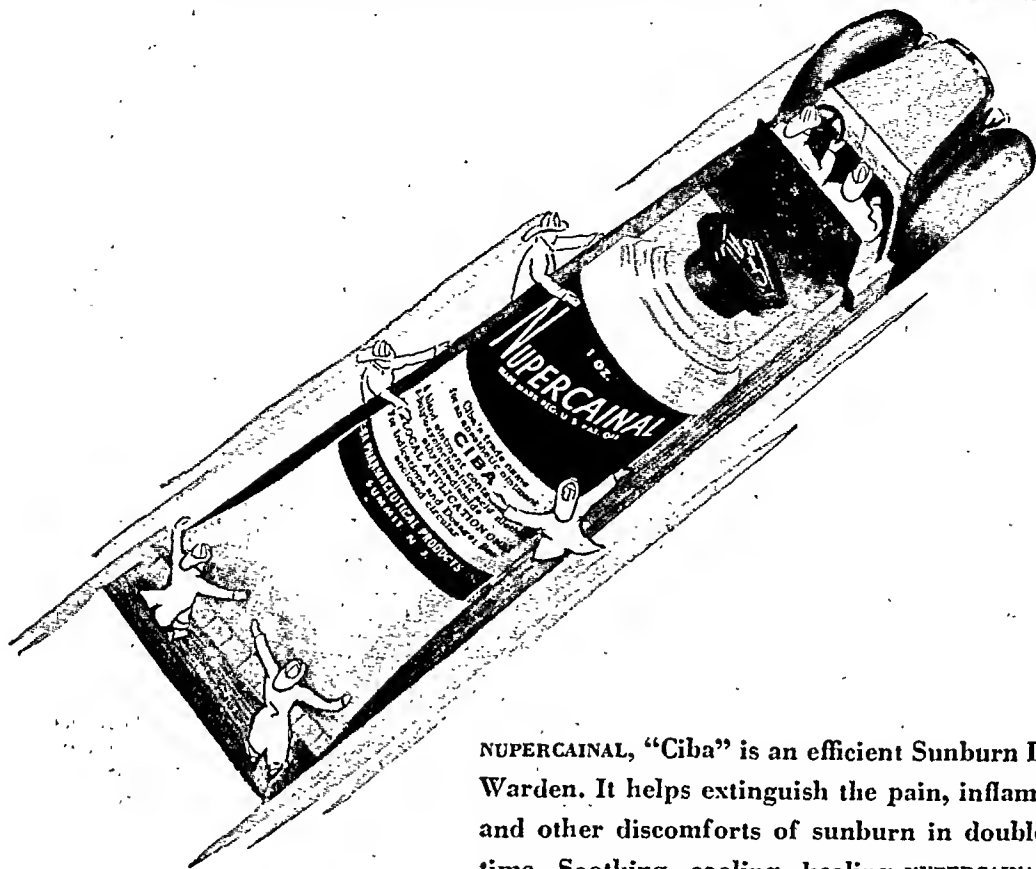
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Joseph Bolivar DeLee
1869—1942

American Journal of Obstetrics and Gynecology

VOL. 43

JUNE, 1942

No. 6

In Memoriam

Joseph Bolivar DeLee

Joseph Bolivar DeLee, long a member of the Advisory Editorial Board of the JOURNAL, born on October 28, 1869, died on April 2, 1942. Paternal preference was for the work of a rabbi but maternal instinct guided the son of Morris and Dora DeLee into and through the professional life of a physician. His graduation in 1891 from the Chicago Medical College, later absorbed by the Northwestern University, was followed by an internship at the Cook County Hospital. Following this, two years were spent in Europe. His specialization and writings indicate that he was largely influenced in the selection and continuation of his activities by Professor Jaggard, and by Professor Ernst Bumm. The premature death of the former gave great impetus to the career of Dr. DeLee who, at an early age, succeeded his former professor at Northwestern University Medical School.

The constructive work of his life took concrete form in the establishment of the Maxwell Street Dispensary in 1894. Five years later he, with others, established a maternity hospital of 14 beds on Chicago's West Side. These facilities soon became outgrown and a new dispensary was built and later a Maternity Hospital of over 100 beds was completed during World War I. On the occasion of the completion in 1931 of the present Chicago Lying-in Hospital on the campus of the University of Chicago, the older hospital was dedicated to the service and medical education of Negroes under the name of the Provident Hospital. The policy of the University of Chicago Medical School was that of having a Department of Obstetrics and Gynecology with full-time salaried teachers. As volunteer professor he was in charge of the Obstetric Service in the hospital until retired as Emeritus Professor at the usual age.

The Chicago Maternity Center was carefully fostered by him as a continuation of the old Maxwell Street Dispensary. The success of

these institutions has in the past been due to the efforts of this leader and to the staff which worked with him and latterly succeeded him. Joseph B. DeLee was an individualist with high professional and personal ideals and endowed with humanitarian instincts. He threw himself wholeheartedly into the development of his native ability and to the skilled application of his professional attainments toward the accomplishment of his ideals. He was hostile to mediocrity and strove for the attainment of perfection.

He filled a position of magnitude in the field of obstetrics which he helped to elevate in its standards; in the field of education, especially visual, where he pioneered in the development of moving pictures, and in the community life, where he blazed trails in bringing the best of obstetric care into homes lacking minimal essentials of living.

His influence was spread widely by the doctors, nurses, and non-professional personnel of the staffs who were under his tutelage. Many students have left his classroom to apply his teachings throughout the States of the Union. He was a star of the first magnitude in the obstetric heavens and only death has dimmed the brilliancy which will continue to illumine the atmosphere of his profession.

An In Memoriam of this leader would be incomplete without mention of the close family ties which assisted him in his early, mature, and later life. This is best illustrated by the formation of the Mothers' Aid group by his sister, Ida DeLee Neuman, who organized the group bearing this name. Since 1904 the Mothers' Aiders have carried on expanding a program of varied activities to support and disseminate the ideas and works of their idol. A feeling of loss pervades his surroundings, but with it there lives a memory of his great service to his profession and mankind which will continue through many decades. This man dies but his influence marches on through decades by his personal contacts, writings, and visual education.

Fred L. Adair.

Original Communications

6

FURTHER STUDIES ON ERYTHROBLASTOSIS NEONATORUM OF OBSTETRIC SIGNIFICANCE*

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ERYTHROBLASTOSIS neonatorum runs much of its course in utero and produces certain manifestations which are of significance to the obstetrician. It is the purpose of this communication to emphasize certain obstetric features revealed by a study of 55 cases, as well as to inaugurate a second period of study to cover five years. The role played by this disease in infantile mortality was stressed in a preliminary report made in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* in 1937. Following the completion of a five-year period of study, an obstetric pathologic analysis of 47 cases was published in *Surgery, Gynecology and Obstetrics* (January, 1942).

Several objectives have been held and of these, early diagnosis of the disease, ante partum if possible, or at the time of delivery from a study of cord blood, has received particular attention. The responsibility has been placed upon the obstetrician and the pediatrician in consultation in order to provide prompt treatment. No longer should one wait for the jaundice to deepen, or the pallor to increase, before providing transfusions of compatible blood. It is hoped that early diagnosis and treatment will reduce the high mortality rate and minimize the damage to the liver, brain, and other organs.

Attention has also been directed toward ascertaining the etiology and pathogenesis of the disease. In this regard, important studies of the Rh factor have been carried out by Levine. Finally, a lesion of the placenta, an intraplacental hematoma, containing normoblasts and erythroblasts, most likely of fetal origin, has been observed in a few cases of erythroblastosis. Such a condition could provide for the transmission of the Rh factor of Landsteiner and Weiner contained in the red cells of the infant, or some other agglutinin as yet unknown, from the fetal circulation to that of the mother. Iso-immunization of the mother is produced, with the formation of anti-Rh agglutinins, as shown

*Read at a meeting of the New York Obstetrical Society, Feb. 10, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

by Levine, Vogel, Katzin and Burnham. These antibodies are then supposed to pass through the placental barrier to the infant where red cell hemolysis is produced. The rather generalized deposition of hemosiderin pigment in the liver, spleen, kidney, and basal nuclei of the brain is evidence of such destruction. Actual damage is also sustained by these organs. Hematopoietic foci persist beyond the normal range, and are generally regarded as a continuation of the embryonal type of blood formation. In general, the degree of involvement is most marked in the hydropic infants, and is present to a less extent in the icterus, anemia, and hemorrhagic diathesis forms of the disease. The bone marrow is hyperplastic, and contains numerous immature normoblasts and erythroblasts which are also to be found in the hemopoietic foci as well as in the circulating blood.

The obstetrician is in a strategic position to influence the destiny of these infants as well as the mothers and fathers. This is of great importance not only from the standpoint of the erythroblastosis, but also with regard to the mother, should she require a transfusion, as is illustrated by Case 3. Furthermore, he will be called upon to advise the parents with regard to future pregnancies.

CLASSIFICATION

The most prominent clinical feature is selected when erythroblastosis is classified as to type, i.e., hydrops, icterus, or anemia. At times this may prove difficult when two or more occur in the same infant. Recently, the author has shown the need for further differentiation of erythroblastosis and has called attention to the hemorrhagic diathesis type of the disease, and an unclassified group. A complete classification of 55 pavilion and private cases* delivered in the Woman's Clinic is shown in Table I. Proper identification has more than academic value, since prognosis varies with each type of the disease.

The term, "hemorrhagic diathesis," refers to a small group of infants having bleeding from the cord, melena, or bloody vomitus, and skin

TABLE I. CLASSIFICATION OF ERYTHROBLASTOSIS NEONATORUM

	NO. OF CASES	FETAL MORTALITY
Hydrops fetalis	17	100 per cent
Icterus gravis	27	45 per cent
Congenital anemia	4	25 per cent
Hemorrhagic diathesis	4	25 per cent
Unclassified cases	3	100 per cent
(Without hydrops, icterus, anemia, or hemorrhagic diathesis)		
Total	55	65 per cent
Missed abortion	4	

*Private cases have been included through the kindness of Drs. Craig, Greeley, Harrar, Hawkins, Jellinghaus, McCandlish, Williamson, Wing, Sackett, and Steele.

petechiae, in whom careful studies of the cord blood, placenta, or autopsy data, reveal the presence of erythroblastosis instead of hemorrhagic disease of the newborn. Of four such cases in this group, three mothers had a history of erythroblastosis in a previous child. In none of these was there jaundice, or hydrops, to overshadow the hemorrhagic diathesis. The following report illustrates a typical case.

CASE 1.—Mrs. C. F., aged 31 years, Irish, para 5-0-0-2, has had five previous pregnancies, the first in 1934 was a normal infant. It was followed by 3 infants with icterus gravis, all of whom died. The last one of these was autopsied at another hospital and the typical lesions of erythroblastosis were present. The fifth child was delivered elsewhere in 1940 and was normal in every respect, and no specific therapy had been given during the ante-partum course.

The ante-partum course of the present pregnancy was uncomplicated and the period of gestation was forty-three weeks. Maternal blood studies revealed that the patient was Rh negative (husband positive), the Wassermann was negative, and there was no maternal blood abnormality. Vitamin K was given intramuscularly (4 mg. of thyloquinone, Squibb) several days before delivery, at which time the maternal prothrombin level was 71 per cent of normal, and the icterus index was 4 units (normal 2 units).

The infant developed fetal distress during the twenty-six hours of labor. Delivery was spontaneous, and the infant weighed 4,350 Gm. (excessive size). It was asphyxiated and required CO₂ and O₂ resuscitation.

Cord blood studies were carried out immediately. A prothrombin concentration of 14 per cent of the adult normal was found. The blood was also Rh positive. The icterus index was 20 units. The red blood count was 3,350,000, hemoglobin 16 Gm., and white blood count 74,100; there were 90 normoblasts and 46 erythroblasts per 100 white cells. Many of the latter were immature leucocytes.

The infant developed multiple skin petechiae soon after birth and on one occasion vomited some bloody mucus. It also had some dyspnea. Immediately after birth, 3 mg. of thyloquinone (vitamin K, Squibb) was administered, and an additional 1 mg. was given the following day because the prothrombin level had fallen to 7 per cent of the adult normal. Three transfusions were given in the first days of life. The nucleated red cells had disappeared from the circulating blood by the seventh day. The hemoglobin and red cell count were maintained at normal levels and the infant was discharged on the twenty-eighth day of life in excellent condition.

The placenta weighed 765 Gm., the cord was stained yellow, and the amniotic fluid had a brownish color. Histologic section showed numerous nucleated red cells in the fetal vessels. The villi were large with some edema of the connective tissue (duration of pregnancy was forty-three weeks).

The unclassified group includes three infants who died in utero, and in whom examination of the cord blood and autopsy disclosed unmistakable evidence of erythroblastosis. Had these infants been born alive, they

may have developed clinical icterus or anemia and then would have been properly classified. This type of erythroblastosis, without hydrops, icterus, and anemia, has also been reported in the literature by Salomonson, DeLange, and Ferguson. As a subdivision of this group, four cases of missed abortion have been included as shown in Table I. They occurred in patients having a history of erythroblastosis, two of whom showed unmistakable evidence of erythroblastosis in the placenta. This is an important finding, since the infants were too macerated for histologic diagnosis at autopsy.

INCIDENCE

The incidence of erythroblastosis (all types) is 1:438, as shown in Table II. Wolfe reports an incidence of 1:568. At present, many

TABLE II. INCIDENCE OF ERYTHROBLASTOSIS (ALL TYPES)

(Indoor, Outdoor and Private Services: Jan. 1, 1933, to Dec. 31, 1941)

YEARS	TOTAL NO. OF CASES	NO. OF PREMATURE AND FULL-TERM DELIVERIES	RATIO
1933, 1934, 1935	7	10,819	1:1545
First 5-year study			
1936	8	3,390	
1937	9	3,443	
1938	8	3,632	
1939	7	3,383	1:438
1940 (Twins 1 pr.)	9	3,672	
Total	41	17,520	
Second 5-year study			
1941	7	3,504	

more cases are being diagnosed than was the case a few years ago. There is no apparent increase in the incidence judging from the fact that from 7 to 9 cases have occurred consistently in the past six years.

Erythroblastosis is responsible for 3.2 per cent of the fetal deaths and exceeds syphilis, sepsis, and hemorrhagic disease as a cause thereof. The lower rate for syphilis is due, no doubt, to prophylactic ante-partum therapy. It is hoped that such an approach will be discovered for erythroblastosis. Prevention of antibody formation in the mother may be such an objective.

DURATION OF GESTATION

The average duration of pregnancy was 36.4 weeks in the hydropic infants, and those with the other forms of erythroblastosis were usually born nearer term. Generally speaking, the nearer term, the milder was the disease, and the better seemed the prognosis as shown in Table III. Excluding the cases of hydrops, the average duration of pregnancy for infants that survived was 39.9 weeks, whereas, in those that died, it was only 38.6 weeks.

TABLE III. THE RELATION OF DURATION OF PREGNANCY TO BIRTH WEIGHT AND FETAL MORTALITY IN ERYTHROBLASTOSIS

	DURATION OF PREGNANCY WEEKS	BIRTH WEIGHT GM.	MORTALITY RATE %
Hydrops	36.4	3,421	100
Icterus	39.2	3,426	48
Anemia	40.2	3,095	25
Hemorrhagic diathesis	39.1	3,842	25
Unclassified	40.0	3,360	100

The average weight of 3,421 Gm. in the infants with hydrops is excessive for the gestation of thirty-six weeks, and has been attributed to the generalized edema. For the other types of the disease, the weights were within the expected range.

PARITY

Most observers, including Potter and Sehumann, have reported erythroblastosis in multiparas. Multiparity is a distinct factor in 85 per cent of the cases as indicated in Table IV. The disease usually ap-

TABLE IV. THE INCIDENCE OF ERYTHROBLASTOSIS IN SUCCESSIVE PREGNANCIES

	TOTAL PREGNANCIES	NUMBER	PERCENTAGE
First pregnancy	52	8	15.0
Second pregnancy	50	26	52
Third pregnancy	31	16	51
Fourth pregnancy	20	8	40
Fifth pregnancy	12	6	50
Sixth or over	8	6	76
Total	173	70	

pears in either the second, third, or fourth pregnancy. Repeated pregnancies serve to increase iso-immunization according to Levine and

TABLE V. PROGNOSIS IN 55 CASES OF ERYTHROBLASTOSIS AS SHOWN BY THE OBSTETRIC HISTORY OF 8 PRIMIPARAS AND 47 MULTIPARAS

	PREGNANCIES BEFORE ERYTHRO- BLASTOSIS			ERYTHRO- BLASTOSIS		PREGNANCIES AFTER ERYTHROBLASTOSIS			
	NO. INFANTS	STILLBIRTHS AND NEONATAL	ABORTIONS	NO.	INCIDENCE*	NO. INFANTS	ABORTIONS	ERYTHRO- BLASTOSIS	
								NO.	INCIDENCE*
Primiparas (8 or 15%)	0	0	4**	8	100.0%	0	2	9	100%
Multiparas (47 or 85%)	92	18	12 (7.1%)	47	30.0%	8	8 (32%)†	9	53%

*Omitting abortions.

**Two were induced.

†Four were missed abortions.

his co-workers. However, 8 or 15 per cent of the patients were primiparas, 6 of which had the severest form of the disease, namely hydrops fetalis.

The recurrence of erythroblastosis in subsequent pregnancies has been found to be 100 per cent in primiparas, a 1:1 ratio. In the multiparas, it is 53 per cent, or a 1:3 ratio, as shown in Table V. Such a dominance suggests a definite hereditary influence which will be discussed under the Rh factor. Sick cell anemia is also believed to be inherited as a dominant mendelian characteristic.

Abortion was not frequent, namely, 7 per cent; although after the appearance of erythroblastosis, it occurred in 32 per cent. There was only one case of habitual abortion, but missed abortion occurred in 4 patients.

RH FACTOR

It has been stated above that women having infants with erythroblastosis appear predisposed to the disease, perhaps on a hereditary basis. However, multiparas may have normal infants after its appearance, as indicated in Table V. Interest centers around a newly discovered blood factor called Rh, which Landsteiner and Wiener found in the red cells of the *Macacus rhesus* monkey. They ultimately showed that the blood of 86 per cent of the random population contained this factor, whereas, the remaining 14 per cent lacked it, and were designated as Rh positive and Rh negative, respectively. The Rh factor is regarded as a dominant mendelian characteristic transmitted by a pair of genes RH and rh. The incidence of genotype RHRH is given as 37 per cent; RHRh is 47 per cent, and rhrh is 15 per cent.

Levine, Burnham, Katzin, and Vogel find that in erythroblastosis 90 per cent of the mothers are Rh negative, and the husbands are Rh positive, just the reverse of the incidence in the random population. The baby is usually Rh positive. They theorize that, under such circumstances, iso-immunization of the mother takes place with the formation of anti-Rh antibodies or agglutinins which pass through the placenta and hemolyze the infant's blood. On this basis they explain the pathogenesis of erythroblastosis. Since erythroblastosis occurs most commonly in the second, third, or fourth pregnancy, the previous pregnancies are thought to have started some iso-immunization of the mother. The stage is now supposedly prepared for the appearance of erythroblastosis in the next offspring.

A consideration of various allelomorphic combinations of the RHRH, RHRh and rhrh genotypes recently described by Landsteiner and Wiener are shown in Figs. 1, 2, and 3.* As can be seen, the father and mother

*These charts have been reviewed by Dr. Karl Landsteiner and approved by him as portraying views published recently in the *Journal of Experimental Medicine*.

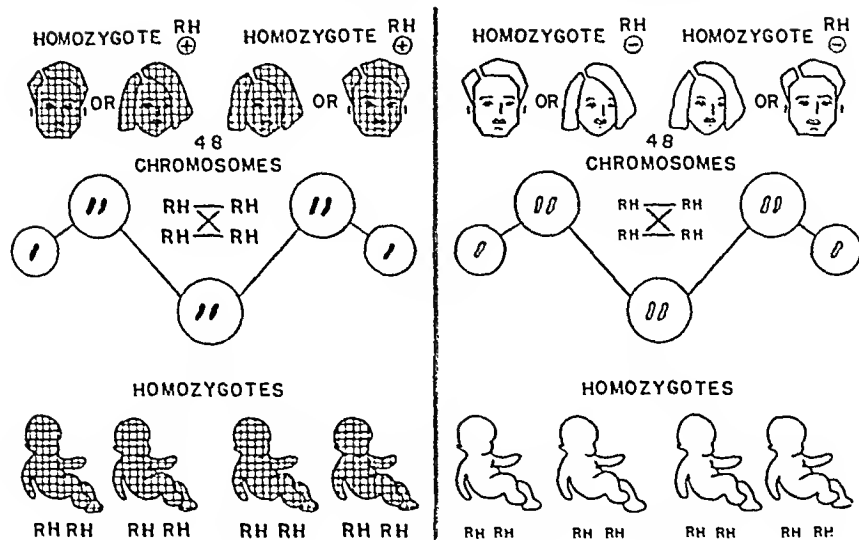


Fig. 1.—Inheritance of the RH agglutinin. (After Landsteiner and Weiner.)

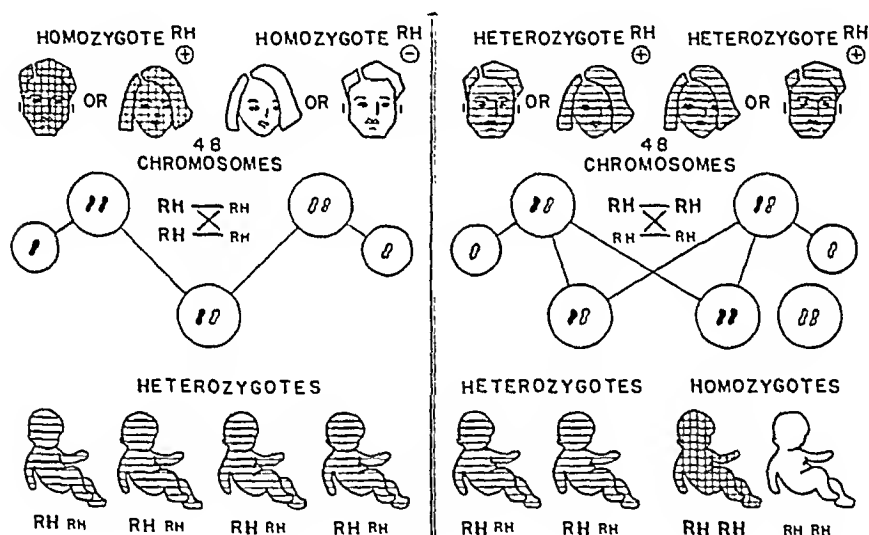


Fig. 2.—Inheritance of the RH agglutinin. (After Landsteiner and Weiner.)

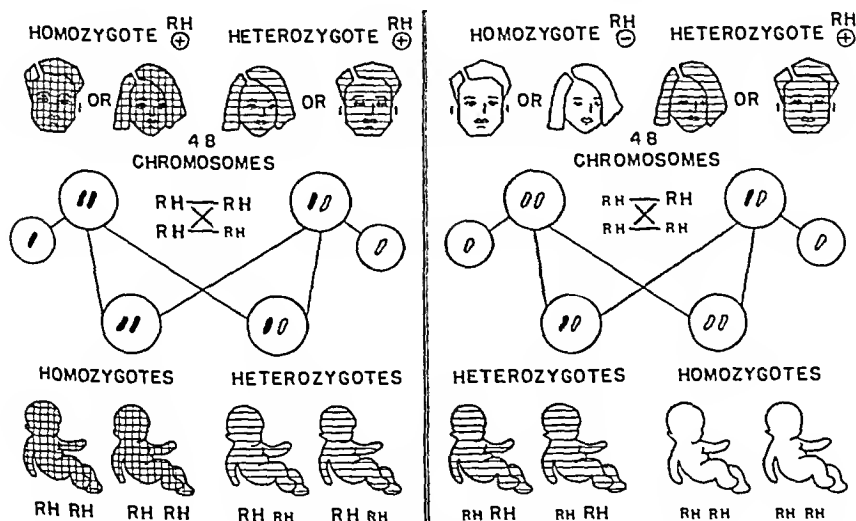


Fig. 3.—Inheritance of the RH agglutinin. (After Landsteiner and Weiner.)

can be homozygous (RHRH or rhrh) or heterozygous (RHrh or rhRH). The offspring will inherit the Rh factor as a dominant mendelian characteristic from either parent and will become homozygous or heterozygous in terms of the factor. Should both parents be homozygous and Rh negative, all of the offspring will be Rh negative and never be subject to erythroblastosis. The chance of such a mating is, of course, remote. However, in a study of nearly 300 cases, Levine, in a personal communication, states that he has never seen the disease occur under such circumstances.

According to Levine and his co-workers, iso-immunization of the mother is possible when she is Rh negative and the father is Rh positive. Her heterozygous and homozygous infants are, therefore, predisposed to erythroblastosis, since 90 per cent of these mothers are Rh negative. However, as shown in Table V, these mothers have a large number of normal infants prior to the first appearance of erythroblastosis, although after its appearance the recurrence is about 50 per cent. The incidence of 50 per cent corresponds with that obtained by Macklin from a study of cases in the literature.

The results of Rh studies by Levine on 14 of our cases are shown in Table VI. The Rh factor was present in the father and infant, and absent in the mother, in 79 per cent of the cases, which corresponds closely to Levine's figure of 90 per cent. However, there were three exceptions (21 per cent), in that the mothers were Rh positive. Of these, two had Rh positive husbands, and the third was Rh negative. These exceptions present a strong argument against the Rh factor per se as the sole cause of erythroblastosis. Agglutinogens A, B, M, N, or some factor as yet unknown may also iso-immunize the mother with the formation of antibodies which could hemolyze the infant's blood. This concept may explain the frequency of physiologic jaundice of the newborn.

When the mother is Rh positive, iso-immunization with the Rh agglutinin should not occur, and therefore, the infant should not have erythroblastosis if Levine's theory is correct. This evidence, together with other information including the birth of normal infants before and after the appearance of erythroblastosis, the occurrence in primiparas not immunized by previous pregnancies, involvement of only one of twins, creates a quandary as to the role played by the Rh factor. It appears that other agglutinogens, known or unknown, as well as Rh, must be considered as causes of iso-immunization as illustrated by Case 2. The inheritance of the Rh factor and its relationship to iso-immunization ap-

TABLE VI. THE RH FACTOR IN 14 CASES

Primiparas					
Father	Rh	Positive	}	2 cases	
Mother	Rh	Negative			
Multiparas					
Father	Rh	Positive	}	9 cases	
Mother	Rh	Negative			
Baby	Rh	Positive			
Father	Rh	Positive	}	2 cases	
Mother	Rh	Positive			
Father	Rh	Negative	}	1 case	Hr factor
Mother	Rh	Positive			
Total				14 cases	

pear to be established, but conclusions as to their role in the etiology of erythroblastosis must be held in abeyance for the present.

The occurrence of erythroblastosis in a mother who was Rh positive and a father that was Rh negative has probably led to the discovery of another atypical agglutinin which has been called Hr by Levine. This factor may explain the occurrence of erythroblastosis in Rh positive women. Of further interest, is the association of the syndrome called "missed abortion." This case will be described elsewhere by Levine and Javert and is given briefly at this time.

CASE 2.—Mrs. K. F., aged 32 years, German descent, para 2-0-2-1, had a negative Wassermann test. The first pregnancy in 1934 was uncomplicated; the child is living and well. The second pregnancy occurred in 1937, and this infant died on the second day of life of icterus and anemia; erythroblastosis was proved by autopsy. The third pregnancy resulted in a missed abortion with the spontaneous expulsion of the fetus in the thirtieth week of gestation. The fetus weighed 700 Gm., and it was too macerated to provide histologic diagnosis. The fourth pregnancy terminated in another missed abortion in September, 1941, the fetus weighing 1,400 Gm. It was also too macerated for histologic diagnosis. However, histologic sections of the placenta showed unmistakable evidence of erythroblastosis as discussed below under "the placenta."

Blood studies by Levine in the last pregnancy showed the mother to be Rh positive, the father Rh negative. Further studies showed that actually another atypical agglutinin had been isolated in the blood of the father, which was named Hr. The mother was Hr negative. At this time, the first-born child was examined and was found to be Rh positive, Hr negative.

Complete examinations of the mother's blood has been otherwise negative with regard to plasma prothrombin, vitamin C levels, hemoglobin, counts, and smears. The husband has also been thoroughly examined from every standpoint, including semen analysis by W. H. Cary. He has a normal fecundating specimen.

This case has important obstetric significance because of the two missed abortions which are placed in the unclassified group (see Table I), until more information is obtained with regard to this entity.

The Rh factor has been regarded by Levine and others as a frequent cause of habitual abortion. Table V shows that only 7 per cent of the mothers had abortions before erythroblastosis appeared. It is assumed that all were Rh negative and the husbands were Rh positive. In the primiparas, the noninduced abortion rate was 20 per cent. Neither of these figures are above the incidence ordinarily accepted. However, it occurred to us to study habitual abortion and 12 cases were analyzed. Of these, 9, or 75 per cent, were Rh positive as were their husbands. Unless additional evidence shows the contrary, early habitual abortions should not be attributed to iso-immunization. The Rh factor as a cause of *missed* abortions is suggested in Case 2 and Table V.

CONGENITAL ANOMALIES

Congenital malformations were found in 12, or 22 per cent, of the infants suffering from erythroblastosis; included were: harelip, cleft palate, spina bifida, bilateral hydrocele, supernumerary finger, cervical rib, urethral stricture, and interventricular septal defect. Weber and Seholtz, Veechi, and Bourret and Lathoud have also reported erythroblastosis associated with congenital anomalies. The incidence of malformations is 40 times greater than Murphy found in the newborn infant. However, he found that when two or more offspring had anomalies, that subsequent offspring had a 50 per cent chance of being deformed. The recurrence of erythroblastosis in multiparas is also about 50 per cent, which suggests very strongly a hereditary basis for the disease.

MATERNAL COMPLICATIONS

The outstanding maternal complications have been the pre-eclamptic type of toxemia and the excessive uterine enlargement, which has been most prevalent in the mothers having babies with hydrops. The relationship of iso-immunization to toxemia was originally reported by Dienst and Ottenberg.

Maternal Mortality.—This was recently reported as none. One mother, however, delivered of an infant with ieterus gravis in 1937, has since died following an operation for ectopic pregnancy.

CASE 3.—The patient was given two transfusions of compatible blood, following which jaundice and anuria, with a rise in the blood nonprotein nitrogen to 116 mg., developed. Because of a persisting anemia (red cell count of 1,990,000), a third transfusion was given from a donor whose blood was shown to be compatible with the recipient's serum at 37° C. A chill occurred. Thereafter, the patient was shown to be Rh negative, and all three donors were Rh positive. The patient died on the fifth postoperative day. Similar cases have been reported in the literature by Levine and his co-workers.

THE PLACENTA

The various weights of the placentas in the various groups were as follows:

Hydrops	1,250 Gm.
Icterus	684 Gm.
Anemia	668 Gm.
Hemorrhagic diathesis	784 Gm.
Unclassified	850 Gm.

The infant-placenta ratio (see Table III for weights of infants in the various groups) was about normal, 6:1 in all but the hydrops group where a ratio of 3:1 was seen.



Fig. 4.—Photomicrograph, low power, showing a laminated intraplacental hematoma containing normoblasts and erythroblasts surrounded by a zone of fibroinoid degeneration.

Histologic studies were performed on 34 placentas (15 hydrops, 12 icterus, 3 hemorrhagic diathesis, 2 anemia, 2 unclassified), and 4 missed abortions. Detailed analysis of these studies will be published elsewhere by Traut and Javert. Hellman and Hertig have published a complete description.

The fetal vessels invariably showed an increase in the number of normoblasts and erythroblasts. Syncytial knots were commonly observed. The Langhans layer was seldom present. Intracapillary erythropoiesis was rarely seen. Basophilia was invariably increased and the fetal vessels often exhibited endarteritic changes. At times the amnion was hyperplastic, and pigmented cells were often present in the chorionic plate. Intraplacental hematomas were observed in 8 cases (Fig. 4). Of 10 hematomas, 7 contained nucleated red cells probably of fetal origin.

The hematomas were often laminated. This finding supports the theories of Dienst, Ottenberg and Darrow, that interchange of incompatible maternal and fetal blood in utero can occur and probably produce icterus in the newborn child and eclampsia in the mother as an antigen-antibody reaction. Of the 8 patients, 62 per cent had toxemia. Doi found erythroblasts in the maternal blood of cases of "pregnancy kidney" and eclampsia.

The villi ranged from normal size to huge edematous structures depending on the underlying type of erythroblastosis. This was most marked in the hydrops type. Under such circumstances the fetal vessels were often reduced in size or were absent. The villi in the icterus cases were smaller in size but now and then were edematous.

The placentas of the hemorrhagic, anemic, and unclassified forms of erythroblastosis also showed the above changes, so that a diagnosis could be confirmed. The placentas of 4 cases of "missed abortion" born to mothers after a previous infant with erythroblastosis were scrutinized with interest. In two of these a definite diagnosis of erythroblastosis could be made. This is extremely valuable since the infants were thoroughly macerated so that diagnosis was not possible at autopsy.

The placenta of single ovum twins (Case 2 recently published by Javert in *Surgery, Gynecology and Obstetrics*) showed unmistakable evidence of erythroblastosis in both identical twins, one having the anemic form, the other unclassified. Dr. Samuel Wolfe reports anemia and icterus in twins.

DIFFERENTIAL DIAGNOSIS

In addition to the classification of erythroblastosis as to type as shown in Table I, it is necessary to differentiate physiologic jaundice, prematurity, intracranial hemorrhage, hemorrhagic disease of the newborn, congenital heart disease, congenital syphilis, sepsis neonatorum, obliteration of the bile ducts, familial acholuric jaundice, Winckel's disease, and hypoproteinemia.

MATERNAL BLOOD STUDIES

Routine examination of the maternal blood in 21 cases showed no significant deviation in the red or white counts or in the blood smear. Anemia of pregnancy was very infrequent. The Wassermann was invariably negative. The maternal blood was usually Rh negative as stated above.

The chemical constituents of the maternal blood reflected the toxemia of pregnancy. The elevation in the values for uric acid and the lowering of the CO_2 , as Stander has reported, was observed. Of interest, was the elevation of the icterus index in several mothers. This may be attributed to hemolysis of the mothers' blood or liver damage accompanying the

toxemia, with impaired bilirubin metabolism, or to actual absorption of excessive amounts from the fetus.

FETAL BLOOD STUDIES

Immediate advantage in making a diagnosis of erythroblastosis in the newborn infant can be obtained from adequate study of the cord blood. It has been our practice to secure blood by aspiration from the umbilical vein of the cord immediately after expulsion of the placenta as shown in Fig. 5. As much as 100 c.c. can be obtained, provided the cord has not been stripped. It is advisable not to do so in these cases in order to provide blood for study. Using the proper technique, blood can be obtained for typing and cross-matching, chemical studies, blood cultures,

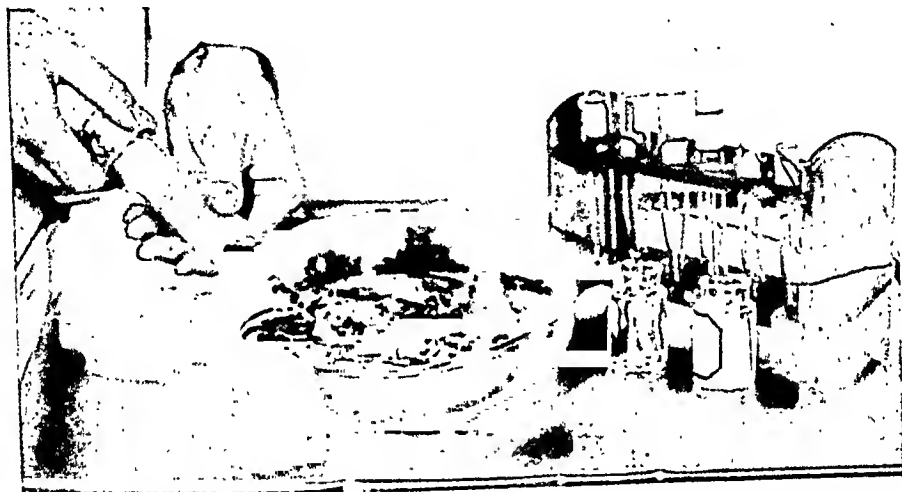


Fig. 5.—Aspirating cord blood directly from the umbilical vein on the fetal surface of the placenta.

vitamin studies and Rh determinations. Such a procedure saves the infant several venipunctures, and avoids delay. Finally, cord blood can be uniformly compared, without considering the day of life the specimen was obtained, as when blood is taken directly from the infant. For example, one of our cases had erythroblastosis, but the first blood smears

TABLE VII. BLOOD STUDIES OF THE UMBILICAL CORD OR ON FIRST DAY OF LIFE*

	R.C.C.	HG (GM.)	C.V.	W.C.C.	N.R.C.	INDEX	
						VOL.	COLOR
5 Hydrops cases	1,51	5.5	25	54,3	43,5	1.5	1.3
6 Icterus cases	3,38	13.1	46	38,4	17,7	1.3	1.4
15 Icterus cases on first day of life	3,09	12.8	--	32.7	14,3	--	1.4
4 Anemia cases	3,5	12.0	--	29.8	13,0	--	1.4
4 Hemorrhagic di- athesis	4,1	16.7	47	43.2	24,5	1.3	1.4
3 Unclassified	4,4	15.0	--	43.8	24,4	--	1.25

*R.C.C., red cell count; C.V., cell volume; W.C.C., white cell count; N.R.C., nucleated red cells.

TABLE VIII. SMEARS OF THE UMBILICAL CORD BLOOD ON FIRST DAY OF LIFE

	NORMO-BLASTS	ERYTHRO-BLASTS	IMMATURE POLYS.	RED CELL DIAMETER
9 Hydrops cases	304	98	34	9.5 μ
6 Icterus cases	71	14	10	8.0
4 Anemia cases	65	12	5	8.0
4 Hemorrhagic diathesis cases	112	19	9	8.1
3 Unclassified cases	106	19	10	8.1

taken on the tenth day of life failed to show any erythroblasts. Cord blood would have done so.

The results of blood studies in the various types of erythroblastosis are shown in Tables VII and VIII. The blood smears were prepared with ordinary Wright's stain and examined at once. The erythroblasts and normoblasts can be readily identified. Their presence is imperative in making an unquestionable diagnosis of the disease.

PATHOGENESIS OF ERYTHROBLASTOSIS

The importance of the inheritance of the Rh factor and iso-immunization have been alluded to above. The iso-immunization theory of Dienst, Ottenberg, and Darrow, has been invoked by Levine, Katzin, and Burnham to explain the hemolysis of the red cells in erythroblastosis. They assume that hemolysis is the initiating cause of the disease, thereby supporting Parsons, Hawksley, and Gittins. Levine and others state that the baby inherits an Rh positive agglutinin from the father, which reaches a maternal circulation that is Rh negative. Anti-Rh antibodies, or agglutinins, are formed, thereby iso-immunizing the mother. These agglutinins return to the infant and produce hemolysis of the red cells. Autotransfusions from the infant, with the passage of known or unknown agglutinogens, may be responsible for the iso-immunization of the mother. The hematomas in the placenta indicate the possibility of such transmission. There are others, including Abt, Von Gierke, Salomenson, Clifford, and Hertig, who regard hematopoiesis as the primary cause of the disease; relegating hemolysis to a secondary role. It is futile to argue which of the two are cause or effect; both are present.

Leaving theory behind, it behooves us to study other features of this interesting disease, and among these is the widespread deposition of hemosiderin pigment. Practically all systems are involved. Intracellular pigment can be seen in the basal nuclei of the brain, the so-called "kernicterus" of Schmorl. It occurs in the skin. The chorionic plate often shows it. It is present in the kidneys and especially in the liver.

Liver insufficiency has been shown to exist both pathologically and physiologically. The hydrops cases have a liver parenchyma consisting of hematopoietic foci up to 20 per cent and even more in some infants. If one adds to this the actual cellular degeneration consisting of intra-

cellular pigment, fatty degeneration, cloudy swelling, or actual cellular necrosis, very little actual functioning tissue remains. This may be a factor in the 100 per cent mortality in these infants. When the organs are extremely macerated, the pigment deposits in the liver may be a distinct aid in the diagnosis of erythroblastosis.

The icterus cases showed less liver involvement as evidenced by hematopoiesis and intracellular pigment to a lesser degree. However, bile thrombi, or collections of bile pigment in the biliary capillaries, were more frequent. This can be expected, since the icterus infants survived longer than the hydrops cases, giving the liver an opportunity to metabolize the excessive bilirubin, which it did not do in utero to the same extent, since the ductus venosus shunts the blood around the liver to the vena cava.

Physiologic evidence of liver insufficiency can be obtained from the lowered values in the cord blood for serum proteins, fibrinogen, prothrombin, and bilirubin, shown in Table IX. The hydrops cases showed a greater deviation from the control than did the icterus cases.

TABLE IX. CHEMICAL CONSTITUENTS OF CORD BLOOD IN ERYTHROBLASTOSIS*

	HYDROPS CASES		ICTERUS CASES		CONTROL
Nonprotein nitrogen	(4)	41.7 mg.	(2)	44.0 mg.	35.0 mg.
Uric acid	(1)	7.8 mg.	(2)	3.5 mg.	3.1 mg.
Chlorides	(3)	563.0 mg.	(2)	444.0 mg.	500.0 mg.
Serum proteins	(5)	3.8 Gm.	(8)	5.1 Gm.	5.5 Gm.
Fibrinogen	(2)	0.05- Gm.	(3)	0.1- Gm.	0.3 Gm.
Prothrombin	(2)	5- %	(7)	10 %	23.0 %
Icterus index	(7)	91 units	(8)	48 units	18 units

*Figures in parentheses denote number of cases studied.

Hypoproteinemia (due to the lowered albumin fraction) has been produced in dogs on a low protein diet by Weech and his co-workers. Nutritional edema developed. Deficits in the erythrocytes and hemoglobin were also observed. The hydrops and focal edema and anemia in erythroblastosis, together with the lowered serum proteins, suggests a lack of proteins which provides a metabolic background for this disease. The important role of the liver in maintaining normal protein levels has been demonstrated further by Weech in other conditions and in congenital syphilis.

That erythroblastosis is a generalized systemic manifestation and is not limited to the hemopoietic system is borne out by the following:

1. The rapid return of the blood picture to normal, with the disappearance of nucleated red cells after the child is removed from its intrauterine environment.
2. The dramatic response to prompt transfusion which provides protein as well as red cells.
3. Recovery without sequelae unless permanent damage has been sustained by the organs of the various systems.

The hemopoietic system apparently recovers rapidly in three weeks according to Josephs. The liver is less fortunate, judging from the reports of liver degeneration by deLange and Arntzenius, Klemperer, Hawksley and Lightwood. These sequelae are less prone to occur if treatment is early and adequate as Sobel has intimated and our experience has shown. Juvenile cirrhosis following icterus gravis has been recorded by Boynton and Wyllie, Braid and Ebbs, and Wilson who has also correlated it with degeneration of the lenticular nuclei of the brain. Kernicterus may be a very significant finding. Strong and Marks have emphasized the mental retardation and spastic diplegia in these infants.

ANTE-PARTUM DIAGNOSIS

The mother often exhibits certain signs and symptoms during pregnancy that may serve as a basis for suspecting erythroblastosis in the unborn child. These are as follows, in approximate order of importance: Multiparity, Rh negative mother, Rh positive father, excessive uterine enlargement, yellow brown amniotic fluid, premature labor, Irish nationality (32 per cent) increased icterus index, erythroblastosis in a previous infant, toxemia, fetal distress before and during labor, intra-uterine death of the fetus, missed abortion, systolic bruit of fetal heart in utero, x-ray of fetus showing halo and Buddha-like habitus.

There is usually no history of sterility which speaks for the normalcy of the ova and sperm. The high incidence in the Irish women is probably due to the fact that they do not use contraception and are prone to have repeated pregnancies and therefore more infants with the disease. The birth of normal infants in about 50 per cent of the multiparas following the appearance of erythroblastosis, and the birth of many normal infants before the disease appeared, suggests that both parents are heterozygous Rh+, or homozygous Rh- and heterozygous Rh+, as indicated in Figs. 2 and 3, so that one or two Rh negative infants are produced which escape the disease. In primiparas, with recurrence of the disease apparently 100 per cent, the parents are probably homozygous Rh positive, homozygous Rh positive and negative, or homozygous Rh positive and heterozygous Rh positive, as shown in Figs. 1, 2, and 3.

TREATMENT OF THE MOTHER AND INFANT

With regard to the mother, every effort should be made to make an intrauterine diagnosis of the disease, using criteria stated above. The titer of anti-Rh agglutinins can be followed in the mother. Toxemia should be anticipated. A diet adequate in protein, minerals, and vitamins is important. Interruption of the pregnancy and cesarean section should only be performed for maternal indication.

In suspected cases, analgesia and anesthesia are interdicted, because intrauterine asphyxia and asphyxia neonatorum are present in a large

percentage of these infants. Fetal distress is, therefore, frequent (56 per cent) and was largely responsible for a high operative delivery rate. Local infiltration is preferred for the episiotomy.

Therapeutic abortion was not performed on the indication of erythroblastosis alone. However, with the recurrence of erythroblastosis as 50 per cent in multiparas and nearer 100 per cent in primiparas, it seems that some consideration should be made. On the same basis artificial insemination with donor and recipient of the same blood group and Rh negative seems to merit investigation.

With regard to the treatment of the infant, all authorities agree on the necessity of prompt and frequent transfusions. As many as a dozen averaging 60 c.c. in amount may be necessary in the first days of life. The whole blood apparently supplies protein, prothrombin and red cells. The dramatic response to this form of therapy indicates correction of an underlying metabolic disorder. With transfusions, the mortality rate has been lowered from 85 per cent to 73 per cent as shown in Table X. In 1941, the mortality rate was lowered still further to 14 per cent; the only deviation in the treatment was the administration of vitamin K directly to the child at birth; from 2-4 mg. were injected intramuscularly. No hydropic infants, however, were born that year.

TABLE X. FETAL MORTALITY IN ERYTHROBLASTOSIS

YEARS	TOTAL NO. OF CASES	MORTALITY	
		NUMBER	PER CENT
1933, 1934, 1935	7	6	85
First 5-year study, 1936-1940	41	29	73
Second 5-year study, 1941	7	1	14
Grand Total	55	36	65

Early diagnosis and prompt treatment are of great importance. Antepartum notes calling attention to the possibility of the disease will make the obstetrician wary at the time of delivery. The golden-colored amniotic fluid, yellow vernix, fetal distress, etc., should arouse suspicion. Cord blood studies should be performed on every case whether obvious or suspicious. Hours and days of delay are to be avoided and immediate transfusion should be given. The mortality rate will be reduced, and the sequelae should be less serious. Advanced and neglected cases die fortunately, although a few survive and develop juvenile cirrhosis, mental deficiency, and spastic diplegia. When the disease is less severe, however, and the treatment is early and adequate, these infants are often normal and healthy.

SUMMARY

A classification of erythroblastosis based on 55 cases is presented.

The incidence of the disease is 1:438.

The mortality rate appears to decrease in infants born nearer term.

Primiparas having infants with erythroblastosis seem prone to have subsequent babies with the disease, whereas, the recurrence in multiparas is about 50 per cent. Such a relationship points to a dominant mendelian characteristic inherited from the parents, and the Rh factor was discussed from this point of view.

An intraplacental hematoma was found in 8 cases. These were of varying age, and contained numerous normoblasts and erythroblasts most likely of fetal origin. Such a lesion provides for the transmission of the Rh agglutinin, or some other factor as yet unknown, from the fetal circulation to that of the mother. In such a manner, iso-immunization of the mother could take place.

The formation of antibodies in the mother, with the passage of these through the placenta into the fetal circulation is probably responsible for the red cell hemolysis and the widespread deposition of hemosiderin pigment which characterizes the disease.

The chief maternal complications were toxemia of pregnancy and excessive uterine enlargement. Congenital anomalies in the infants were frequently observed. The relationship of erythroblastosis to missed abortion was seen in several patients.

Early recognition of the disease, in the delivery room aided by studies of the cord blood, affords an excellent opportunity for prompt treatment. Histologic studies of the placenta are confirmatory.

Damage to the internal organs, particularly the liver, is borne out by pathologic and physiochemical studies.

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DISCUSSION

DR. ALEXANDER A. WEECH.—Dr. Javert's observations have dealt with many features which I, as a pediatrician, have had no chance to observe and am therefore not able to discuss. It is better that the occasion should be taken to introduce items which come within the pediatrician's sphere of observation.

Discovery of the association between the Rh antigen and erythroblastosis is among the most brilliant findings of medical literature in recent years. The association is so impressive as to carry conviction of etiologic relationship. Like Dr. Javert, however, I feel that we do not yet understand fully all of the features which

belong to the disease. The Rh antigen exists on the surface of the red blood cells; so far as I know, it has not been demonstrated in any other tissue cells. The reaction between antibody and antigen is manifestly one of intravascular hemolysis and the result is severe anemia. We are entitled to ask whether or not such a reaction can explain the widespread lesions of the disease. The brain may be severely damaged. Infants who die may exhibit stained basal ganglia (kernikterus); infants who survive may later show various types of cerebral palsies. We do not yet have a satisfying explanation of the mechanism of this cerebral injury. Anemia, which does not respond to iron or liver therapy and which is relieved only temporarily by transfusion, often persists for many months. It seems impossible that Rh antibody can persist in the infant circulation for so long a time. One is led to inquire what can be the cause of such long-lasting and apparently hypoplastic anemia. Dr. Javert has reported histologic evidence of severe liver damage in these infants. I can confirm his finding on the basis of analyses of serum from infants who have not died. The serum bilirubin in these cases almost always reacts directly to the Van den Bergh test. The type of bilirubinemia is therefore different from that encountered in physiologic jaundice. The presence of directly reacting bilirubin in the serum is generally interpreted as evidence that bile is regurgitating from the bile ducts into the blood stream, that is, it implies damage or destruction of liver cells. The factors responsible for this hepatic injury are not yet understood.

I must not close these remarks without mentioning the chief concern which haunts the pediatrician when he is asked to treat one of these infants. There is no doubt that prompt and repeated transfusion will often result in the saving of life. Is the treatment justified if the infant is destined to become a cerebrally defective child? Dr. Katharine Merritt, my colleague at the Babies Hospital, has recently assembled our experience on this point. Among 12 infants who survived the initial period of icterus gravis, 9 are healthy and 3 are defective. We have sought, so far without success, to discover what signs or findings in the afflicted infant might presage the final outcome. We can only state at this time that neither the total serum bilirubin nor the amount of directly reacting bilirubin is a reliable index upon which to base prognosis.

DR. LYMAN BURNHAM.—I would like to emphasize the danger of transfusion in the mothers of these babies. This was one of the original clinical observations which gave rise to the theory of iso-immunization as the cause of erythroblastosis. This danger consists of destruction of the transfused blood, resulting in anuria, uremia, and frequently death. It is caused by the same antibodies in the mother which bring about destruction of the baby's blood in utero, namely, the anti-Rh agglutinins, in 90 per cent of the cases.

Such transfusion accidents have occurred three times in one hospital in the past two years and have accounted for three deaths in the Metropolitan area in the past month of January.

Therefore, when erythroblastosis is present, has been present, or may be present, the mother's life will be jeopardized by transfusion unless special precautions are taken. These consist of using Rh negative blood for the Rh negative mothers, together with the compatibility test as modified by Dr. Levine.

We now know that, in addition to erythroblastosis, iso-immunization accounts for some of the hitherto unexplained cases of anemia of the newborn, fetal death in utero, unexplained stillbirths or neonatal deaths, and possibly some of the cases of habitual abortion. Hence, transfusion should also be avoided in these suspicious cases, if possible. The use of plasma will tide over many a patient where blood was formerly thought to be required.

DR. HAROLD MIXSELL.—We have had several cases of this disease at the Woman's Hospital. I am happy to say that we diagnosed them fairly early. We

believe in immediate transfusion. From the clinical standpoint, we make our diagnosis from the family history, for the condition certainly occurs in families in the second, third, or fourth pregnancy and usually in prematures.

DR. ANDREW A. MARCHETTI.—More emphasis should be placed on the size and weight of the placenta. In the hydrops type of erythroblastosis, it is particularly important. Here the ratio of the weight of the placenta to the baby is usually 1:3, whereas in the icteric type and that with congenital anemia, as in normal pregnancy, the ratio is about 1:6. Where a large placenta is found in relationship to the baby, the placenta should be studied with much more care.

In the normal placenta we find very few nucleated red cells and normoblasts. When the number of these cells is considerably increased, or when one finds even one erythroblast, suspicion should be aroused. Seldom, if ever, do we find normoblasts and erythroblasts in the laminated types of placental hematomas associated with normal pregnancy. There were 8 cases in which we found numerous erythroblasts and normoblasts in hematomas and in every instance the baby had erythroblastosis.

DR. WILLIAM H. CARY.—I joined Dr. Javert in investigating the fertility of some of the husbands in the cases he reported tonight. These patients were all highly fertile and the male specimen showed in its morphology nothing significant, in my opinion, which would aid in determining the etiology of the disease.

DR. JAVERT (closing).—We are not quite as pessimistic about the future of these infants as Dr. Weech is. I think he is basing his statements in part on past performance, which means beginning treatment on the third, fourth, or fifth day of life. We are stressing early treatment one or two hours after birth. Under such a regimen I think these infants will show fewer sequelae. The sequelae Dr. Weech has mentioned, namely, cirrhosis of the liver and lenticular degeneration in the brain, are, however, extremely important, and the occurrence of mental retardation has been pointed out by a number of investigators.

Normoblasts in the blood smear on the second or third day of life may occasionally be found, particularly in premature infants. It is seldom, however, that normoblasts are seen at this time in normal, full-term infants. The rate of maturation of nucleated red cells in the blood stream is so rapid that unless a diagnosis of erythroblastosis is made from cord blood, it is sometimes difficult to do so in three or four days. It is thought also that the rate of disappearance of the nucleated red cells may serve as a basis for prognosis, as well as the bilirubin levels which Dr. Weech mentioned. For example, if a child is born with 200 nucleated red cells in the cord blood, they may be reduced to 100 by the third day, to 25 by the fourth day, and at the end of the first week there may be none at all. Consequently, the gradual disappearance of the nucleated red cells may provide a basis for prognosis.

Dr. Burnham brought up the question of transfusion in pregnancy, as well as in cases of erythroblastosis. There were two mothers in the group who received transfusion. One developed a typical eclamptic seizure during the administration of the blood, the nonprotein nitrogen rose to 70 and the uric acid to 12, and the patient was considered as having eclampsia of a post-partum type. She survived. There has been another patient.

The importance of the Rh factor in sterility is an extremely important question. On the other hand, the fertility of this group of patients is extremely high, as Dr. Cary has stated. These mothers have had repeated pregnancies, so I wonder if the Rh factor per se has any actual significance as far as sterility is concerned.

END RESULTS IN THE TREATMENT OF CARCINOMA OF THE CERVIX*

A FIFTEEN-YEAR REPORT, 1921-1936

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ON TWO previous occasions, in 1931 and in 1936, the senior authors published five- and ten-year end-results obtained in the treatment of carcinoma of the cervix on the Gynecological Ward Service at Jefferson Medical College Hospital.^{1, 2}

The first report embraced a study of 63 patients seen between Sept. 1, 1921, and Sept. 1, 1925, of whom 57 received treatment, 4 with combined surgery and irradiation and 53 with irradiation only. The absolute salvage, patients alive and apparently free of carcinoma when the report was made, was 14.2 per cent and the relative salvage was 15.7 per cent. The relative five-year salvage in this group was 20.7 per cent. The term "five-year salvage" includes those additional patients who had survived treatment for five years or more but had eventually died, either of carcinoma or of intercurrent disease. The follow-up of this group was 96.8 per cent.

The second report added 93 additional patients observed from Sept. 1, 1925, to Sept. 1, 1930, creating a total of 156, of whom 146 were treated, between 1921 and 1930. This survey showed an absolute salvage of 19.2 per cent, a relative salvage of 20.5 per cent, and a relative five-year salvage, as previously explained, of 25.3 per cent. The follow-up figure at this time was 96.1 per cent.

The present study adds 137 patients seen, of whom 131 were treated between Sept. 1, 1930, and Sept. 1, 1936, a grand total for the fifteen-year period of 293 patients seen and 277 treated, with a follow-up figure of 97.2 per cent (Table I). Approximately 7 per cent of the

TABLE I. PATIENTS OBSERVED, FOLLOW-UP, 1921-1936

	TOTAL	FOLLOW-UP	PER CENT
Patients seen	293	285	97.2
Patients treated	277	271	97.8

lesions were classified histologically as adenocarcinoma, the remainder being squamous cell type.

*Read at a meeting of the Obstetrical Society of Philadelphia, Jan. 8, 1942.

Sixteen patients were untreated for various reasons. Ten were in Group 4 and were considered too far advanced for treatment with one exception; this patient signed a release and was treated elsewhere. Five patients in Group 3 signed releases, of whom 2 were subsequently treated elsewhere. One patient in Group 5 signed a release.

Of the 8 untraced patients, 2 were in Group 4 and untreated as just mentioned; 4 were in Group 3 and were lost sight of soon after treatment; all are undoubtedly dead. Three, one in Group 2 and 2 in Group 3, had survived treatment seven, eight, and twelve years, respectively, when last seen or heard from. These latter 3 are considered as dead for statistical purposes but efforts are constantly being made to establish proof of their demise.

A larger group of patients carefully observed over a longer period of time permits of the comparative study of various interesting features relative to grouping, age incidence, types of treatment with variations in technique, and numerous other problems concerned with the management of cervical carcinoma. Much that has been said in general in our previous reports need not be repeated in detail but merely commented upon except where further discussion is enlightening.

EXTENT OF INVOLVEMENT

From the beginning we have consistently used the classification of the late Henry Schmitz in estimating the extent of involvement. It is simple, direct and in our opinion more comprehensible than the classifications suggested either by the American College of Surgeons or by the Health Organization of the League of Nations. The personal equation can never be entirely eliminated in any system of physical examination, but the probability of error is perhaps decreased if a less complicated plan is followed. Our entire series of patients, therefore, have been grouped consistently, and no attempt has been made to re-classify them in accordance with the League of Nations "Atlas," for we doubt the accuracy of such a revision in retrospect. Each patient when primarily seen has been grouped in accordance with our best judgment, and this grouping has been maintained for the duration of that particular patient's life. In other words, if a Group 3 patient has shown unusual regression following treatment, we have not seen fit to reclassify her as a possible Group 2, because confusion might result all along the line if this procedure were followed repeatedly. If renewed activity of the lesion is seen after primary irradiation, and further treatment is instituted, that patient's initial classification remains the same. In Group 5 we have placed all patients whose primary treatment has been elsewhere. This includes not only irradiated patients but also those who exhibited carcinoma of the vaginal vault following panhysterectomy or who showed evidence of recurrence elsewhere. This plan has simplified our classification considerably.

As shown in Table II, early cases (35) constitute barely 12 per cent of the patients observed. This figure varies little from that noted in our previous reports. The vast majority of the patients (238) exhibited advanced lesions (Groups 3 and 4), constituting 81 per cent of the series, while 20 of the patients (6.8 per cent) had received primary treatment elsewhere (Group V). These figures are discouraging, for

TABLE II. EXTENT OF INVOLVEMENT (SCHMITZ CLASSIFICATION)

GROUP	NO.	PER CENT
1	5	1.7
2	30	10.2
3	213	72.6
4	25	8.5
5	20	6.8

they would seem to show, in our experience at least, that patients seen with a relatively early lesion are comparatively rare. It cannot be denied, however, that errors in judgment may put patients in Group 3, when they might conceivably have been placed in Group 2. Parametrial induration and even fixation may sometimes represent an inflammatory reaction that recedes with treatment; it is this possibility that can well give rise to the controversy about reclassification.

AGE INCIDENCE, PARITY, RACE

Reference to Table III calls attention to one fact that cannot be over-emphasized, the astonishing proportion of patients who exhibit cervical carcinoma before they attain the age of forty. The prevalence of the disease is so often associated in the mind of the physician with the later decades of life that the possibility of an earlier appearance is discounted. Thus valuable time is lost in diagnosis and institution of treatment. As a matter of comparison, the present figure of 27 per cent is somewhat lower than that noted in our previous report which was 29.4 per cent. The youngest patient seen was a twenty-two-month-old infant; the youngest adult was twenty-two and the oldest patient eighty-four.

TABLE III. AGE INCIDENCE, PARITY, RACE

DECADE	NUMBER	PER CENT
1- 9	1	0.3
10-19	0	0.0
20-29	10	3.4
30-39	68	23.2
40-49	87	29.7
50-59	80	27.3
60-69	42	14.3
70-79	4	1.3
80-89	1	0.3
Youngest, 22 mo.; oldest, 84		
27 per cent under age of 40		
Nulliparas	25	8.5
Negroes	29	9.8
Jewish	3	1.0

It would be superfluous to present statistics relating to the appearance and duration of symptoms prior to treatment. Irregular vaginal bleeding, both pre- and postmenopausal, generally accompanied with discharge, has usually been present for periods of time, ranging anywhere from a few months to a year and a half before carcinoma was eventually discovered and treated. Neither should it be necessary to repeat the familiar story of delay in investigation for which both the patient and the doctor alike must share responsibility; delay in diagnosis because of undue modesty, apprehension, lack of consultation, failure of adequate examination, and faulty selection of treatment. Too often abnormal bleeding is assumed to be of a functional nature and hormonal therapy is instituted without thorough pelvic investigation and elimination of organic disease. It must be conceded, however, that in exceptional instances cervical carcinoma may develop rapidly, and even extensively without the occurrence of subjective or objective symptoms and signs. Hence the desirability of routine pelvic examinations with frequent biopsies is unchallenged. Catharine Macfarlane³ and her group have shown what can be accomplished in this respect. The importance of prophylactic biopsy with cauterization or trachelectomy as indicated should be constantly stressed. In our own experience this has revealed unsuspected carcinoma in several instances.

The percentage of nulliparous patients observed is 8.5; in the previous presentation, the figure was 5.7; both these figures have a significance that should be appreciated. The percentage of negro patients has decreased from 13.4 per cent to 9.8 per cent. It is doubtful whether or not this variance has any particular meaning. With regard to the Jewish race, however, it is striking to observe that there were only 3 such in the series, 1 per cent.

RESULTS OF TREATMENT

We have frequently commented upon the fact, as have many others, that freedom from signs and symptoms of cervical carcinoma for a period of five years following treatment is in no sense a criterion of "cure." We have seen recurrence as late as ten years after the initial treatment; for that reason we prefer to use the term "salvage" when speaking of patients who have survived for five years or longer after therapy. On the other hand, as one of us pointed out in a paper presented three years ago,⁴ prolongation of life for five years and longer has not infrequently resulted from the successful repetition of irradiation for recurrence.

Our statistics therefore are presented on the following basis:

1. *Present-Day Salvage*.—a. The number of patients alive following treatment when the observation period is reported, based on the total number of patients actually seen (absolute per cent).

- b. The number of patients alive following treatment when the observation period is reported, based on the number of patients actually treated (relative per cent).

2. *Five-Year Salvage*.—The added number of patients treated during the observation period who have survived for five years or longer but

have eventually died of carcinoma, of an intercurrent condition, or as in some instances, of an entirely different malignant growth (relative five-year per cent). Some patients in this category most certainly do not die of their original carcinoma, but this cannot be definitely stated unless proved with autopsy; hence it is unwise to include such individuals as actually salvaged carcinoma patients, but attention may properly be called to the fact that in this group, a certain number of women presumably did not die as a result of their initial malignancy.

Table IV presents the results secured in the treatment of all patients, irrespective of grouping and embracing all forms of therapy. It will be seen that the absolute salvage is 12.9 per cent; the relative salvage is 13.7 per cent; and the five-year salvage is 23.1 per cent. Five years ago, the percentages were 19.2, 20.5, and 25.3, respectively. Ten years ago the percentages were 14.2, 15.7, and 20.7, respectively. This tends to show that as survivors grow older the mortality rate is influenced by those diseases incident to old age, and not necessarily due to recurrent carcinoma, unless definitely proved. This assumption is borne out by the fact that the five-year salvage figure is relatively constant. Furthermore, some patients who have reacted well to treatment die of intercurrent causes before the five-year observation period has elapsed.

TABLE IV. GENERAL RESULTS OF TREATMENT, ALL GROUPS

Of 293 patients observed, 38 are alive from 5 to 20 years	12.9 per cent (absolute)
Of 277 patients treated, 38 are alive from 5 to 20 years	13.7 per cent (relative)
26 additional patients survived from 5 to 15 years after treatment, establishing a 5-year salvage of	23.1 per cent (relative)
(8 of these 26 patients presumably did not die of carcinoma, and 3 untraced patients were alive 7, 8, and 12 years, respectively, when last seen)	
Primary mortality (4 patients)	1.4 per cent

The percentage of surviving patients who were over 40 years of age when they received their initial treatment is about twice as large as the corresponding percentage of survivors under 40. In other words, the older patients have done twice as well as regards survival as have the younger ones.

Table V shows the results tabulated in percentages, as expressed in Table IV, but arranged to show the results obtained in each group. The results secured in the so-called "early cases" (Groups 1 and 2) are obviously better than those exhibited by the series as a whole, as is to be expected. In Group 1, of 5 patients observed and treated, 2 are alive

TABLE V. RESULTS OF TREATMENT, ALL GROUPS

GROUP	PATIENTS		ALIVE	ABSOLUTE SAL- VAGE PER CENT	RELATIVE SAL- VAGE PER CENT	5-YEAR SAL- VAGE PER CENT
	SEEN	TREATED				
1	5	5	2	40.0	40.0	3—60.0
2	30	30	8	26.6	26.6	13—43.3
3	213	208	26	12.2	12.5	46—22.1
4	25	15	0	0.0	0.0	0—0.0
5	20	19	2	10.0	9.5	2—10.0
Total	293	277	38	12.9	13.7	64—23.1

10 and 20 years, respectively; an additional patient survived ten years and her death, at the age of 64, was attributed to apoplexy, but there was no autopsy.

Of 30 patients in Group 2 observed and treated, 8 are alive from five to nineteen years. Five additional patients in this group survived from six to twelve years, of whom 4 definitely died of carcinoma, while one is untraced after eight years of good health.

Of the 213 patients in Group 3, 208 were treated and 26 are alive from five to nineteen years. Twenty additional patients survived from six to fifteen years after their initial treatment, of whom 11 are definitely known to have died as a result of cervical carcinoma. Of the remaining 9 patients, 4 were reported to have died of cardiovascular disease at an advanced age, as was a fifth patient, but since she had been operated upon a year before her death for a granulosa cell tumor of the ovary, this pathologic lesion may have been contributory to her death. The sixth patient died of carcinoma of the ovary fifteen years after treatment for carcinoma of the cervix, and at autopsy no trace of carcinoma could be found in the uterus. The seventh patient died of diabetic coma, apparently free of cervical carcinoma. The eighth and ninth patients are untraced but were free of carcinoma when last seen, seven and twelve years after treatment, respectively. Recent investigation leads us to believe that they are still alive, but they have not been definitely located at this writing.

None of the patients in Group 4 survived the five-year period.

In Group 5, two patients were alive eight and ten years after treatment, respectively, out of 20 patients seen and 19 treated.

Four patients died primarily as a result of treatment, a mortality of 1.4 per cent. Autopsy was performed in each case. In two instances, pelvic peritonitis developed promptly, with death occurring on the seventh and tenth postoperative days, respectively. These women were between 40 and 50 years of age and the post-mortem examinations revealed pyogenic processes in the uterus and adnexa in addition to acute suppurative pelvic peritonitis. Radium therapy was undoubtedly the factor in producing or at least activating virulent pelvic infection. The other two deaths occurred in older women, 54 and 64 years of age. One died on the eighth postoperative day, the other on the twenty-first. In neither case was peritonitis found at autopsy. Both exhibited advanced cardiovascular and renal disease in addition to the pelvic findings of advanced carcinoma. Consequently these fatalities could scarcely be ascribed to the radium applications. Specific experience with pelvic peritonitis resultant from radium therapy has been detailed in a previous communication.⁵ It may be stated that even the most careful preoperative care and preparation cannot invariably exclude the possibility of the development of postirradiation peritonitis with potential fatality. The part that interstitial irradiation may play in such an outcome is problematical.

TREATMENT WITH SURGERY AND IRRADIATION

Surgery was a factor in the treatment of but 8 patients. Four of these were treated primarily by us, between 1921 and 1923. Immediate panhysterectomy was carried out in 2 patients in Group 1. One was followed with recurrence in the vaginal vault three years later, irradiation with radium and x-ray was successful, and the patient has now sur-

vived for twenty years. The other died nine months later. Two patients in Group 2 received preliminary irradiation with radium, followed by panhysterectomy and subsequent irradiation; one died of recurrence in one and one-half years; the other survived for six years.

Four patients had primary panhysterectomy elsewhere. Their original grouping is problematical, and they were accordingly placed in Group 5. None received preliminary irradiation as far as we know. Three of them treated by us, 2 with radium and one with x-ray for vaginal vault recurrence within a year of the primary operation, survived less than a year. The fourth patient, treated with both radium and x-ray, is now alive eleven years (Table VI).

TABLE VI. TREATMENT, SURGERY AND IRRADIATION, 8 PATIENTS

GROUP	PATIENTS	PRELIMINARY IRRADIATION	OPERATION	SUBSEQUENT IRRADIATION	ALIVE	RELATIVE SALVAGE PER CENT
1	2	1, Yes; 1 No	Comp. hyst.	Yes	1	50
2	2	Yes	Comp. hyst.	Yes	0	0
5	4	No	Comp. hyst.	Yes	1	25
Total	8				2	25

Thus no patient was treated solely by surgery. The very prompt recurrence noted in each instance is mute evidence of the inadequacy of the surgery performed on these patients. It was probably not of the type of which Lynch and Bonney are capable, and serves to stress the point that if a surgical decision is made, it must be carried out by one qualified to perform a truly radical operation based on the premise of an undoubtedly early lesion.

TREATMENT WITH IRRADIATION

Irradiation was used solely in the treatment of 269 patients. The results are tabulated in Table VII, according to groups, contrasting the

TABLE VII. TREATMENT, IRRADIATION ONLY, 269 PATIENTS

GROUP	PATIENTS	ALIVE	REL. SALVAGE PER CENT	5-YEAR SALVAGE	
				PATIENTS	PER CENT
1	3	1	33.3	2	66.6
2	28	8	28.5	12	42.8
3	208	26	12.5	46	22.1
4	15	0	0.0	0	0.0
5	15	1	6.6	1	6.6
Total	269	36	13.3	61	22.6

present-day salvage with five-year salvage. It can readily be seen that these figures are but little altered from those presented in Table V, since the number of patients in whom surgical treatment was combined with irradiation therapy is relatively insignificant.

Of more interest is the manner of employment of irradiation therapy with the results achieved. During the observation period upon which this report is based, treatment underwent several changes. From 1921 to 1931 radium was used principally, most often as a single primary application after the experience of our first year. External irradiation with the x-ray was employed more or less sporadically during this time,

subsequent to the local use of radium, and most often in instances of recurrence. From 1931 to 1934, it was used much more frequently and systematically, subsequent to the radium applications, and as a regular plan of therapy. During this time, too, the x-rays were used more widely in markedly advanced cases with the exclusion of radium. In 1934 and 1935 external irradiation first began to be used as a preliminary procedure and 12 patients were so treated. Ten received x-ray therapy both before and after the use of radium during this time. Since 1936, preliminary external irradiation has been instituted as a routine procedure of choice, and this plan is in vogue at present. Hence this report is based on an observation period of fifteen years, during which radium was generally used primarily and x-ray therapy was utilized afterward as a supplemental factor in the majority of the patients treated.

Table VIII presents the various measures of radiation therapy employed and shows the number of patients treated by each plan, together with the contrasted present-day and five-year salvage. No attempt has been made to indicate the effect of the varying forms of treatment upon each group, since so relatively few patients were in Groups 1 and 2. It will be noted that those patients treated with both radium and x-ray present superior survival rates. It would seem that those patients receiving preliminary irradiation show a higher salvage rate, but it must be remembered that these were the patients who were treated more recently by this method. Only when another five-year observation period has elapsed can we evaluate this newer technique.

TABLE VIII. TYPES OF IRRADIATION TREATMENT AND RESULTS

IRRADIATION	PATIENTS	ALIVE	RELATIVE SALVAGE	SURVIVORS	5-YEAR SALVAGE
Single radium	115	17	14.7%	29	25.2%
Repeated radium	22	2	9.1%	3	13.6%
X-ray only	33	0	0.0%	0	0.0%
X-ray and radium	99	17	17.1%	26	26.2%
Subsequent	77	11	14.2%	19	24.6%
Preliminary	12	4	33.3%	4	33.3%
Both	10	2	20.0%	3	30.0%

We note in Table IX the influence that reirradiation for recurrence has had on the survival rate. Comparison of these figures with our previous report on this subject three years ago shows that at that time 46.2 per cent of our patients then alive from five to sixteen years following initial radiation had survived because of repetition of treatment during the observation period, while the balance of the survivors at that time (53.8 per cent) had received but a single course of therapy. This

TABLE IX. INFLUENCE OF REIRRADIATION

Patients treated, 269; Survivors, 36

22 patients (61.1 per cent) are alive from 5 to 18 years without evidence of recurrence, following a single course of radiation therapy, a relative salvage of 8.1 per cent
14 patients (38.9 per cent) survived 5 to 18 years because of re-irradiations during the observation period, increasing the relative salvage to 13.3 per cent

lowered trend of ultimate survival in the reirradiated group is readily understandable, when one considers that patients receiving repeated treatments for recurrence are likely to die sooner.

CARCINOMA OF THE CERVICAL STUMP

Among 293 patients, carcinoma of the cervical stump was encountered 14 times, an incidence of 4.7 per cent. This includes all patients seen, irrespective of when the supravaginal hysterectomy had been performed. The time period varied from one to twenty-five years. Four of the patients have survived treatment from eight to fourteen years, a present-day salvage of 28.5 per cent, while 3 additional patients survived six, nine, and eleven years, respectively, a five-year salvage of 50 per cent. Two of the latter patients died of recurrent carcinoma; the third, who survived eleven years, presumably died of cardiovascular disease, but there was no autopsy. This is the same patient who was previously mentioned as having been operated upon a year prior to her death for a granulosa cell tumor of the ovary. Further discussion relating to the problem of cervical stump carcinoma is not pertinent to this report, other than to note the fact that the results of treatment have been better than with carcinoma of the cervix in general. Our views relative to the occurrence and possible avoidance of this condition, together with management, have been expressed in previous presentations^{6, 7} (Table X).

TABLE X. CARCINOMA OF CERVICAL STUMP

Carcinoma of cervix		293 patients
Carcinoma of cervical stump		14 patients
Incidence		4.7 per cent
Present-day salvage (8 to 14 years)	4	28.5 per cent
Five-year salvage (6 to 11 years)	7	50.0 per cent

TECHNIQUE OF IRRADIATION

The transition from radium therapy alone to its correlation with external irradiation has been mentioned briefly in a preceding paragraph. The technique, with variations, should be described as a matter of record.

Radium Application.—During the observation period embodied in this report (1921 to 1936), intracervical and interstitial applications were employed, using (1) a 50 mg. capsule of radium, screened with 0.3 mm. of silver and 1.0 mm. of brass, enclosed in black rubber tubing of 2 mm. thickness, and placed in the cervical canal; (2) 8 needles, each containing 12.5 mg. of radium, screened with 0.3 mm. of Monel metal and generally inserted about the periphery of the growth. This combination totaled 150 mg. of radium which was held in position with gauze packing for the time requisite to insure varying dosages. From 1921 to 1924 the average dosage was between 2,000 and 2,200 mg. hr.; from 1924 to 1927, it averaged 3,000 mg. hr.; during 1927 and 1928, the average was 4,300 mg. hr.; from 1928 to 1936 it was decreased to 3,600 mg. hr. because of many severe reactions. Beginning in 1935, an additional 50 mg. capsule, screened with 0.5 mm. of platinum, was obtained to replace the brass capsule or to use in conjunction with it sometimes.

This armamentarium continued in consistent use until early in 1938 when three 50 mg. capsules screened with 1.5 mm. of platinum and ten 10 mg. needles screened with 0.5 mm. of platinum were secured to replace the former equipment. Several more years of observation will have to elapse before we can evaluate what change, if any, has resulted from this alteration in screening.

X-Ray Application.—The late Willis F. Manges and his associates J. T. Farrell, Jr., and R. Manges Smith directed the technique of external irradiation throughout the period of time covered by this report. Since 1938 this phase of the treatment has been supervised by Karl Kornblum and his co-workers.

Prior to 1927 massive doses were given at a single sitting at right angles to one of 3 or 4 pelvic ports. The amount given was that which the skin would tolerate, and the entire course was completed in three or four days. The factors were 3 ma. at 170 to 200 kv., filtered through 0.5 mm. of copper and 1.0 mm. of aluminum at 50 cm. skin-target distance, through ports 16, 19, or 20 cm. square. The total dosage delivered through each port varied from 800 r. to 2,100 r.

After 1927 the fractional method was followed, treatment being directed through 4 ports, 2 anteriorly and 2 posteriorly, with the factors as previously mentioned. The object then was to deliver 100 per cent of the skin erythema dose into the depths of the pelvis in two weeks by giving treatment on alternate days until the saturation level was reached. Treatment was then continued two more weeks. The total dosage delivered through each port by this method varied from 1,400 to 1,500 r. This plan was followed with but little variation throughout the remainder of the observation period.

It was about this time that external irradiation began to be used more or less as a routine procedure prior to the application of radium. In 1938 and 1939, still employing the same factors, multiple portals averaging four in number, two anteriorly and two posteriorly, continue to be employed, cross-firing on the uterus. Two such areas are treated daily, each receiving 200 r. (measured in air). The treatments are continued until a well-marked erythema is obtained which in general will occur with a total of 1,600 to 2,400 r. to each portal, and such a series requires about three weeks for completion.

When we began to use preliminary external irradiation, the radium was applied near the termination of the x-ray treatments or soon afterward. Now the radium application is delayed from two to three weeks, because reactions were sometimes too severe when the internal and external irradiation coincided too closely. There is no doubt that the x-rays diminish local necrosis, slough and infection; pain and bleeding are frequently relieved as well. On the other hand, if too long a time elapses before applying the radium, vaginal vault contractures may occur that render radium insertion difficult. It remains to be seen what the five-year results will be with this present technique, but the present trend of three- and four-year survivals augurs well.

In cooperation with the x-ray department, we are about to initiate transvaginal or so-called cone therapy in conjunction with preliminary external irradiation and the local use of radium. The apparently satisfactory results attained by Behney and others with this method are convincing, and we are eager to institute this feature as a part of our routine.

HISTOLOGIC GRADING AND PROGNOSIS

We have no reason to change our views with regard to the impracticability of attaching prognostic significance to the histologic grading of carcinomatous lesions of the cervix. Radiosensitivity is relative and radiocurability is not an equivalent term. The response to irradiation is not only contingent upon the biologic processes that are constantly going on in all the tissues within range of treatment but also, to an appreciable extent, upon the age and physical status of the patient and the amount of irradiation administered. Consequently it is probable that prognosis depends to a far greater extent upon the clinical characteristics of the lesion and its subsequent response to irradiation than upon primary microscopic gradation. The majority of our surviving patients exhibited lesions of a low or intermediate grade of malignancy and patients with an anaplastic, highly malignant type of tumor cell frequently reacted badly to irradiation. Those with adenocarcinoma did relatively poorly.

COMMENT

Time and space will not permit discussion of numerous interesting problems peculiar to individual patients in this series, occurrences which perhaps are not an uncommon experience in any similar group. Some have been touched upon in passing, as the occurrence of multiple malignancies and the coincidental finding of pelvic inflammatory disease. Granulosa cell tumors of the ovary were removed from 2 patients, ten years after successful radium therapy for cervical carcinoma. Instances of carcinoma developing in cervixes that have been subjected to previous repair have occurred and several times malignancy has been discovered by routine cervical biopsy or amputation; coexistence with syphilis is not infrequent. Odd metastases have been observed; annoying bladder and bowel lesions have been seen. Fistulas are known to have occurred in at least 12 per cent of our patients; how many more is problematical as the exact circumstances attending the deaths of patients in remote areas are not always clear. The list could be prolonged; much material is available for further associated investigation.

An intimate study such as this, pursued over a period of twenty years, is bound to be discouraging in view of the low survival rate presented. The personal contact with so many hopelessly ill patients, and with their grieving relatives and friends creates impressions that can never be erased. When experience tells us that one out of four or five patients will perhaps remain well for five years or more, and that if we follow such survivors sufficiently long, death from recurrent carcinoma will eventually claim half of them, it cannot leave one light-hearted. Year after year we see the same large group of women coming to us with far-advanced disease because so often ignorance and indifference have resulted in late diagnosis, this in spite of vigorous cam-

paigns to spread the knowledge required to insure an early diagnosis and the institution of effective treatment.

But there is the brighter side, the supreme satisfaction that comes with seeing those who improve and remain well. It is these successes that keep alive that spark of effort, which induce us to go on and on, constantly trying to improve our methods, not only by seeking new departures in treatment, but by analyzing and profiting by the failures of the past.

SUMMARY

1. An analysis of a series of 293 patients with carcinoma of the cervix observed on the Gynecological Ward Service, Jefferson Medical College Hospital, from Sept. 1, 1921, to Sept. 1, 1936, of whom 277 were treated, is presented, based upon a follow-up study of 97.2 per cent of the patients seen and of 97.8 per cent of those treated.

2. An absolute present-day salvage rate of 12.9 per cent, a relative present-day salvage rate of 13.7 per cent, and a relative five-year salvage rate of 23.1 per cent are presented. These are contrasted with rates of 19.2 per cent, 20.5 per cent, and 25.3 per cent respectively, published in 1936; and with rates of 14.2 per cent, 15.0 per cent, and 20.7 per cent respectively, published in 1931.

3. Various phases of the analysis are discussed and compared with the previous reports, together with the exhibition of pertinent data.

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255 SOUTH 17TH STREET
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1831 DELANCEY STREET

DISCUSSION

DR. CHARLES A. BEHNEY.—This paper represents more than twenty years of work by one individual, a unique series in which comparisons are of greater value than when the observations of various persons are recorded.

The extent of involvement in Dr. Scheffey's group of patients is fairly typical of similar series in the average hospital. One series which varies materially from it is that from the Woman's Medical College Hospital, with its astonishingly large proportion of cases in Groups 1 and 2. I have always suspected that these latter figures were less the result of the routine examinations of apparently healthy women, than the outcome of years of persistent teaching by Dr. Macfarlane and her associates, of hundreds of students in the importance of routine pelvic examinations and frequent biopsy. These after graduation searched diligently for early lesions of cancer, which when found were promptly referred to the Woman's Medical College for treatment.

At the end of five years, 23.1 per cent of patients were living and free of symptoms of cancer. Fifteen years later, only 12.9 per cent were still well, a deterioration in results amounting to about 44 per cent. Several years ago Kimbrough and Tompkins studied the records of the gynecologic service of the University Hospital, to compare the ten-year salvage of carcinoma of the cervix, with that at the end of five years. They found that in the second semidecade, 17 per cent of the patients who had been well after five years died of carcinoma or some other disease. Likewise, in the series of Ward and Sackett, there was a 27 per cent loss, and in Lynch's series, one of 17 per cent in the second five years after treatment. Bonney reports a decrease of 23 per cent in his salvage, five to ten years after *radical hysterectomy* for carcinoma of the cervix. It would be very interesting and enlightening, if ten- to twenty-year results in Grade 1, 2, 3, and 4, respectively, could be compared. It would be logical to find less deterioration in the statistics of Grades 1 and 2 than in those more advanced, since dissemination would be less probable before treatment was applied.

It is obvious that a woman who had been afflicted with carcinoma of the cervix, and who is well five years after being treated, cannot be guaranteed freedom from subsequent recurrences. Yet, I doubt whether in a series of patients of a similar age, suffering from coronary disease, cerebral hemorrhage, nephritis, etc., any method of treatment will permit 25 per cent to be free from symptoms five years after treatment. The patient who had cancer of the cervix, furthermore, can enjoy a comparatively unrestricted life during this five-year period. This point should lend a more cheerful aspect to cancer of the cervix, and if more generally known, should remove some the prevalent horror for this disease.

DR. CATHARINE MACFARLANE.—Knowing the difficulty of keeping in touch with ambulatory patients in a large city, I was particularly impressed with the fact that Dr. Scheffey has been able to follow-up 97.8 per cent of his cases. This demonstrates the enthusiasm of the Department of Gynecology of Jefferson Medical College and the efficiency of that Hospital's Social Service Department as well.

The fact that less than 12 per cent of Dr. Scheffey's patients were in Groups 1 and 2 of the Schmitz classification, once more calls attention to the tragic delay which elapses in so many of these cases between the first symptom and adequate treatment. It once more raises the question of the responsibility for this delay. In a series of 83 cases of cancer of the cervix admitted to the gynecological service of the Hospital of the Woman's Medical College, the delay period ranged from three days to five years. The average is approximately eleven months. A study of the records of these cases revealed the fact that in 77 per cent the delay was due to the *patient's* ignorance, indifference or fear, while in 23 per cent the responsibility for the delay rested upon the family physician. Prescribing without examining, examining without inspecting the cervix, failure to make a biopsy, lack of a good pathologist were the chief factors in the physician's delay. It would seem that these factors were preventable.

After watching the success attending the efforts of the Committee on Maternal Mortality of the Philadelphia County Medical Society, under Dr. Philip Williams' leadership, I have felt for a long time that a similar committee devoted to the study of the delay period in cancer of the uterine cervix might accomplish a great deal to eliminate the element of physicians' delay in these cases.

Further study of Dr. Scheffey's paper reveals the fact that in 115 patients receiving a single radium treatment, the five-year salvage was 25.2 per cent, whereas in 99 patients receiving both x-ray and radium, the five-year salvage was 26.2 per cent. The close similarity of these percentages raises the question as to whether or not the x-ray plays an essential role in the treatment of cancer of the cervix. It would be interesting to have these cases analyzed according to the stage of the disease

present. It would also be interesting to compare Dr. Scheffey's statistics in this respect with those of other large clinics. In view of the fact that in the Hospital of the Woman's Medical College we invariably use both radium and x-ray, I am not in a position to express an opinion.

DR. GEORGE LAWS.—Will Dr. Scheffey tell us how many cases of carcinoma of the cervix passed through the large clinic in the Jefferson Hospital and did not go into the ward and how many early cases were picked up at the clinic? In our work we have been limited in our treatment of patients with the advanced disease. After failing to cure them, we are not able to continue to treat them on account of lack of facilities.

DR. SCHEFFEY (closing).—Dr. Macfarlane's suggestion regarding the formation of a committee to reduce the mortality from cervical carcinoma, along the lines of the work that has been accomplished in the field of maternal mortality, is indeed a valuable one and worthy of further thought.

My impression is that the results obtained during the past four or five years, which of course do not influence the present report, will show improvement, since external irradiation with x-ray has preceded local radium applications. It was only during the last year or so of this report that such a technique was employed more or less routinely. It seems to me that the present three- and four-year survivals indicate a more hopeful trend.

What I especially wanted to point out tonight was: First, the number of patients now alive from five to twenty years after treatment; second, the additional number who survived treatment for five years or more, but had eventually died either from recurrent or unarrested carcinoma, or from some intercurrent disease. In the latter instance, in the absence of an autopsy, we have classified these deaths as due to carcinoma even though such a presumption may not have been correct. On this basis the five-year salvage has remained more or less constant, ranging from 22 to 25 per cent throughout the observation period.

Dr. Behney has referred to the findings of Kimbrough and Tompkins, who compared the salvage at the expiration of five- and ten-year periods. It so happens that I discussed that paper, and our results closely approximated theirs: 18.8 per cent of the patients who had been well after five years died thereafter of carcinoma or of an intercurrent condition.

In answer to Dr. Laws I would say that our patients reach the gynecologic service either by direct reference to the hospital or through the out-patient department. If other arrangements can be made, we try not to admit hopelessly ill patients (Group 4). With an active but limited service of 27 beds, such a policy is necessary, but we take care of every patient that we think can be helped. Others must be sent to institutions designed to provide care for incurable cases of any sort, and this is not infrequently resorted to with patients who have received the maximum treatment that we have been able to provide for them without avail.

THE CONTRACTIONS OF THE HUMAN UTERUS DURING PREGNANCY AND LABOR*

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RECENT studies of the motility of the nongravid human uterus have revealed the presence of a cycle of myometrial activity under the control of the ovarian hormones.¹⁻³ The contractions in the follicular phase of the menstrual cycle are characterized by small amplitude, short duration, short intervals between contractions, and high tonus. In the luteal phase, which follows ovulation, the contractions gradually increase in amplitude and duration but decrease in frequency and tonus. The maximum amplitude is reached as a rule at the onset of menstruation after which there is a gradual return of the small waves. This cycle has been reproduced in castrates by administering the ovarian hormones in the natural sequence: first estrogen alone and then together with progesterone.⁴ The possibility that the change from the follicular to the luteal phase contractions represents a *progravid* phenomenon, analogous to the secretory transformation of the endometrium, stimulated this study of the motor activity of the uterus during pregnancy and labor, which was begun in October, 1939.

The misconception has arisen in some quarters that the uterus, under the alleged inhibitory influence of progesterone, remains quiescent during pregnancy. While this may be the case in the rabbit, as claimed by Knaus, Reynolds and others, the evidence is conclusive that progesterone† augments the contractility of the human uterus.²⁻⁴ Braxton Hicks,⁵ in 1871, demonstrated by abdominal and vaginal palpation that the human uterus undergoes spontaneous intermittent contractions throughout pregnancy. Schatz,⁶ in the following year, published the first records of labor pains obtained by means of an intrauterine bag. This method has since been used successfully by a number of workers in studying the effects of drugs on the puerperal uterus. The bag, however, is not a practical means of recording the contractions of the pregnant uterus because of the danger of abortion and infection. Technical

*Read at a meeting of the New York Academy of Medicine, Section of Obstetrics and Gynecology, November 25, 1941.

†More accurately, progesterone in the absence of estrogen has little if any effect on the human uterus.⁴ It is the combined action of progesterone and estrogen that stimulates myometrial activity. Since the corpus luteum and the placenta produce both hormones simultaneously, pure progesterone effects can occur only under experimental conditions in castrates.

difficulties also arise in maintaining sufficient pressure within the balloon probably due to the extreme distensibility of the gravid uterus.

The first attempt at external hystero-graphy was made by Schaeffer⁷ in 1896, but his apparatus was too cumbersome. Rübsamen,⁸ in 1920, introduced a second method which, while ingenious, was inaccurate in use. The first dependable apparatus for external hystero-graphy was designed by Dodek⁹ in 1932 in connection with a study of the action of drugs and anesthetics on the parturient uterus. Since then a number of modifications of his technique have appeared.¹⁰⁻¹³ Most of the present external methods are based on the principle that the contraction of the uterus results in a forward displacement of the anterior abdominal wall. The degree of displacement can be measured by placing a suitable tambour, usually pneumatic or mechanical, in contact with the abdomen in the region of the umbilicus. Fenning¹⁴ has recently perfected an extremely sensitive electrical method of recording the abdominal wall movements.

MATERIALS AND METHODS

The abdominal tambour employed in this study is of the pneumatic type and is essentially an inexpensive and simplified modification of the Dodek apparatus. It has proved to be highly sensitive and very satisfactory in use. The details of the set-up are shown in Fig. 1. A total of 283 recordings were obtained from 81 patients, white and colored, ranging in age from 16 to 40 years, who were attending the prenatal clinics or residing on the obstetric wards of the Morrisania City Hospital. Both normal and abnormal cases of pregnancy and labor were included. The greatest number of tracings from a single patient was 23, the least one. Thirty women were pregnant for the first time; the remaining 51 patients had from 1 to 14 previous pregnancies.

In some patients weekly observations were made throughout pregnancy, beginning with the third month when the uterus had risen sufficiently above the symphysis to make contact with the abdominal tambour. In other cases, daily recordings were made at various stages of pregnancy for one or more weeks. Tracings were also obtained from women in labor, term, and premature, and from women in whom labor was being induced by various means (castor oil, quinine and pituitrin, stilbestrol, pregnenolone, rupture of the membranes, and bougies). The indications for the inductions were toxemia of pregnancy, post-term pregnancy, premature rupture of the membranes and heart disease. One case of hydatid mole was also studied. A few observations were made in the early puerperium, but contractions were rarely recorded after the fifth day because of uterine involution. The recordings were made for a minimum of thirty minutes with the patient lying quietly but comfortably in bed. Most tracings ran for one hour and in some cases as much as three hours.

RESULTS

The results of this study will be presented by describing several typical cases which illustrate the important features.

ECTOPIC PREGNANCY

CASE 1.—M. H., white, 38 years of age, para ii, entered the Vanderbilt Clinic* for primary dysmenorrhea. Menses previously were regular every twenty-eight days. The last period, however, began Feb. 5, 1940. Pelvic examination on May 2, 1940, failed to reveal any signs of pregnancy. The following kymographic records were made with an intra-uterine balloon: Fig. 2, A (May 2, 1940) showed the presence of minute

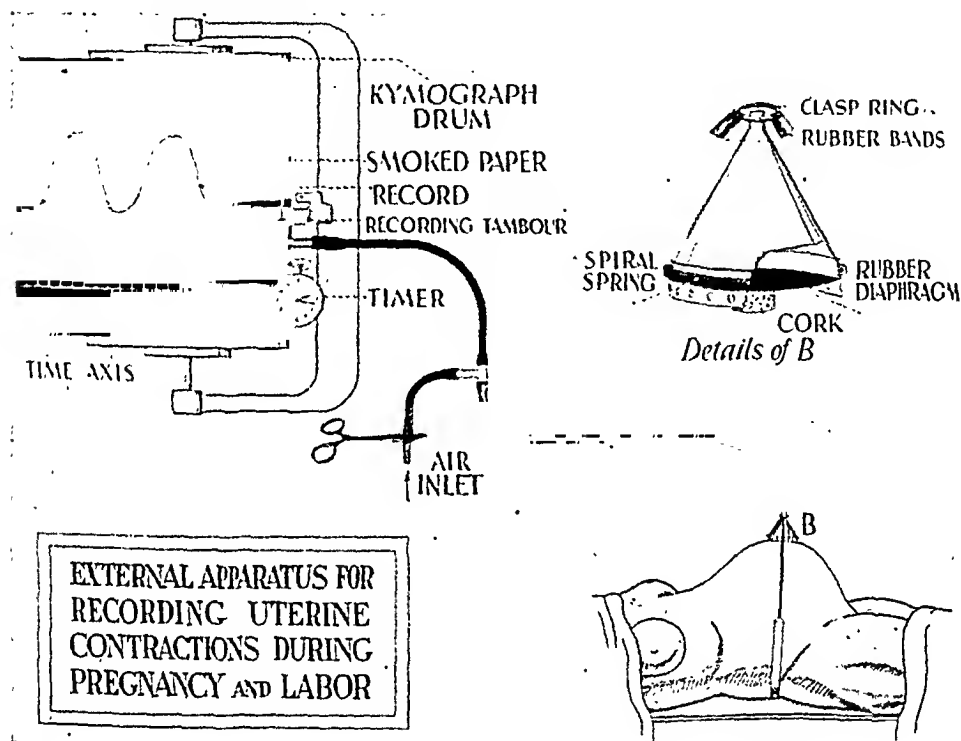


Fig. 1.—The abdominal tambour consists of an aluminum funnel, $2\frac{1}{2}$ inches in diameter at its base, which is covered by rubber tissue to form a diaphragm. A leak-proof attachment of the diaphragm is secured by cementing it to a tightly-fitting, rubber-covered spiral spring (used in contraceptive pessaries) around the base of the funnel. Direct contact of the diaphragm with the skin is avoided by interposing a perforated metal band. Contact is made by means of a cork cemented to the diaphragm. If this were not done, perspiration would make the diaphragm adhere to the skin and the body heat would raise the air pressure in the conducting system. The abdominal tambour is held in place by means of a canvas belt and stout rubber bands which hook on to a clasp ring at the neck of the funnel. Pressure tubing connects the abdominal and recording tambours, but a T-tube is interposed to permit adjustment of the pressure. The T-tube is clamped in an interval between contractions (determined by palpation).

barely discernible waves. The balloon pressure was low (40 mm. of mercury) despite the introduction of an additional volume of air. We now recognize these findings as being characteristic of early gestation. Fig. 2, B (May 16) and C (May 20) revealed a similar picture but the intramuscular injection of pituitrin (20 I.U.) evoked a prompt tonus rise and the appearance of moderate size contractions. Fig. 2, D (May 23) showed large prolonged contractions of the type usually seen a few days preceding and during menstruation. The patient now complained of mild abdominal pains and slight vaginal bleeding. These

*I am indebted to Professor Benjamin P. Watson for permission to include this case.

symptoms suddenly became markedly aggravated on May 26, 1940. Laparotomy two days later disclosed a ruptured left tubal pregnancy. The uterus was slightly enlarged; a small fetus, placenta, old and recent blood clots were found free in the peritoneal cavity.

The exact time of rupture was uncertain, but from analysis of the clinical and pathologic pictures, it is probable that a mild rupture occurred some time between May 20 and 23, and a second but more ex-

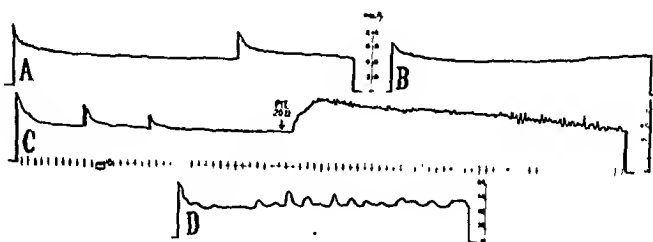


Fig. 2.—(Case 1.) Contractions recorded by intrauterine balloon in a case of tubal gestation. *A*, *B*, and *C* before rupture reveal practically no contraction waves and low pressure which is not increased by introduction of additional air because of extreme distensibility of uterus. Pituitrin, however, produces increased tonus and moderate size contractions (*C*). Following rupture large uterine contractions are recorded without use of pituitrin (*D*). Time intervals indicated in minutes.



Fig. 3.—(Case 2.) Uterine contractions recorded by external hystero-graphy at monthly intervals during a normal pregnancy. *A*, Third month; *B*, fourth month; *C*, fifth month; *D*, sixth month; *E*, seventh month; *F*, eighth month. Note totally arrhythmic pattern of motility during pregnancy. Two types of contraction waves are present: (1) large prolonged waves (Braxton Hicks contractions) and (2) small waves of short duration. Sharp vertical thrusts (*F*) are caused by fetal movements. Time intervals indicated in minutes.

tensive rupture took place on May 26 when the symptoms suddenly became acute. The registration of the large contractions for the first time in Fig. 2, *D* is accounted for by the diminished uterine distensibility following the disturbance of the gestation. Prior to the tubal rupture uterine contractions were recorded only after the administration of

pituitrin. It is evident that the intrauterine balloon is not a satisfactory method of hystero-graphy during gestation.

NORMAL PREGNANCY

CASE 2.—M. T., white, 26 years of age, had one previous full-term pregnancy. Expected date of confinement June 10, 1940. The following series of tracings were made by external hystero-graphy at monthly intervals during the major portion of an uncomplicated pregnancy: Fig. 3, *A* (Dec. 15, 1939) during the third month, *B* (Jan. 19, 1940) fourth month, *C* (Feb. 14, 1940) fifth month, *D* (March 13, 1940) sixth month, *E* (April 24, 1940) seventh month, and *F* (May 15, 1940) eighth month. Delivery occurred spontaneously on June 4 after a six-hour labor.

This series, which is typical, demonstrates that the human uterus normally contracts in a totally arrhythmic fashion throughout pregnancy. There are two types of contraction waves:

1. Large prolonged arrhythmic waves of one to five minutes' duration which are easily palpated and are often perceptible to the patient as a cramp-like sensation or pain (false labor pains). These are the Braxton Hicks contractions. They probably represent mass contractions in which all the uterine muscle fibers participate. At times these large arrhythmic waves occur at frequent intervals and rarely they may be absent in a two-hour period of observation.

2. Small arrhythmic waves not exceeding one minute in duration. They are seldom present during normal labor, cannot be palpated, and are rarely noted subjectively. They were only recently described by Douglas Murphy¹⁵ and may represent regional myometrial activity.

Periodic variations in contractility corresponding to the time of menstruation (if pregnancy did not exist) have not been observed. Nor has any progressive increase in myometrial activity been noted as gestation advanced. The contractions throughout pregnancy are totally irregular.

INDUCED PREMATURE LABOR

CASE 3.—D. M., white, aged 33 years, a multipara, was hospitalized because her pregnancy was complicated by chronic nephritis. A series of daily tracings (Fig. 4) was obtained during a twelve-day period preceding induction of premature labor. The last menstrual period began July 15, 1939, and the date of expectancy was April 22, 1940. The first tracing was obtained on March 3, 1940. Labor was induced March 14 during the thirty-fifth week of gestation by the oral administration of 100 mg. of stilbestrol in 5 divided doses at hourly intervals followed by castor oil, quinine, and pituitrin. Labor began after the fourth dose of pituitrin and terminated spontaneously eight hours later in the birth of a living premature infant.

This group of tracings demonstrates the rather abrupt change from the markedly irregular contractions of pregnancy to the rhythmic pattern of motility in labor. The contractions shown in Fig. 4, *L*, which were recorded a few hours preceding the induction, occurred regularly at eight-minute intervals and were painless. Rhythmicity, however, is

not an invariable forerunner of labor. For example, Fig. 3, *D* showed a group of 6 contractions occurring at two-and-one-half-minute intervals but this rhythmic activity was not maintained, and labor did not start until eleven weeks later.

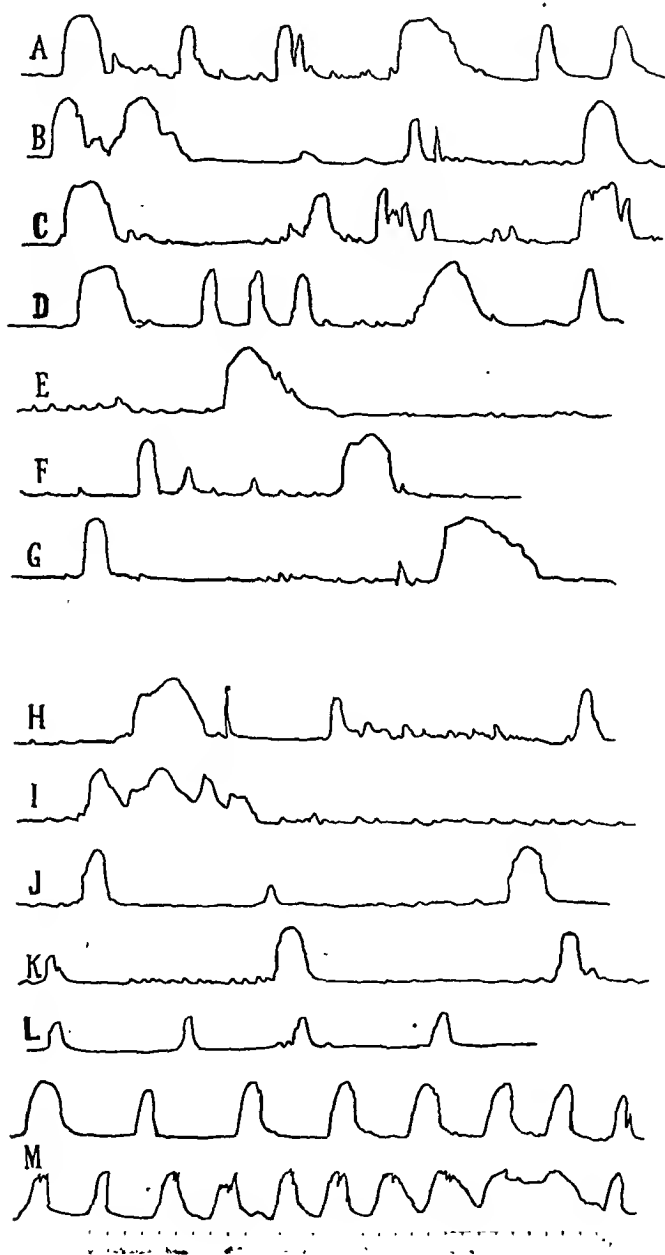


Fig. 4.—(Case 3.) Daily tracings during eighth month of pregnancy beginning twelve days before the induction of premature labor for chronic nephritis. Totally arrhythmic pattern of contraction with painless large and small waves before labor (*A-L*). During labor (*M*) all contractions are large, painful and rhythmic. Spontaneous delivery occurred ten minutes after end of tracing.

What do these transient episodes of rhythmic myometrial activity during pregnancy signify? It would seem that they represent attempts by the uterus to evacuate its contents. It is well known that the uterus

is capable of expelling the fetus at any stage of gestation. Why it usually does not before term is reached is not known, but it may be assumed that some additional factor is necessary either to release the energy of the uterus or more likely to give it the extra stimulus it may require. These rhythmic episodes bear a striking resemblance to the contractions that follow the administration of pituitrin (Fig. 5, *C*). The role of the posterior pituitary in initiating parturition has received scant consideration, since it was demonstrated that labor can occur in hypophysectomized animals. Recent evidence, however, points to the

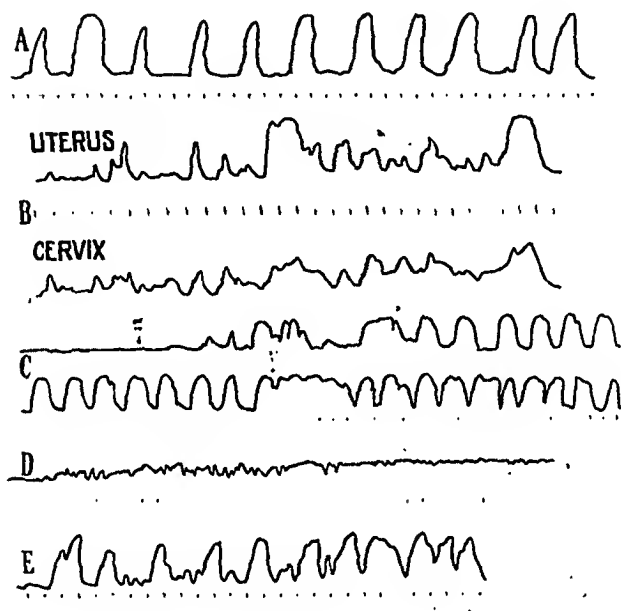


Fig. 5.—*A* (Case 4), reveals large rhythmic contractions in labor at term. *B* (Case 5), is a simultaneous recording of uterine contractions and the changes in the position of the cervix during the thirty-first week of pregnancy. Note that the cervix is retracted or pulled up with each contraction. Retraction during pregnancy leads to important preparatory changes for labor. *C* (Case 6), demonstrates clonic and tetanic contractions induced by pituitrin in a multipara near term. Note similarity of clonic contractions to labor pains. *D* (Case 7), reveals small, frequent arrhythmic contractions in a case of uterine inertia during labor. Large contractions absent. *E* (Case 8), demonstrates the typically arrhythmic large and small pregnancy contractions in a case of hydatidiform mole.

probability that oxytocic substances are produced in other parts of the brain,¹⁶ and it may therefore be necessary to reconsider this hypothesis which has much to recommend it.

NORMAL TERM LABOR

CASE 4.—E. S., white, aged 39 years, a multipara at term, was in labor. Fig. 5, *A* reveals the uterine contractions seven hours after the spontaneous onset of labor. The membranes were intact and the cervix was 2 fingers dilated. The pains were fairly regular and occurred at approximately four-minute intervals. Spontaneous delivery took place three hours later. The appearance of these rhythmic contractions is the same whether labor occurs at term, past term, or prematurely and whether it begins spontaneously or is induced.

THE RELATION OF THE CERVIX TO THE CONTRACTIONS OF THE UTERUS

CASE 5.—D. M., white, 33 years of age, a multipara, was thirty-one weeks pregnant. Fig. 5, *B* is a simultaneous record of the contractions of the uterus and the changes in the position of the cervix. The cervical movements were registered by leading a silk thread sutured at one end to the cervix through a pulley arrangement to a muscle lever writing on the smoked drum. It will be noted that the cervix was retracted or pulled up with each uterine contraction and that it dropped down when the uterus relaxed. This phenomenon was recorded as early as the twentieth week of gestation and was seen during the remainder of pregnancy, labor, and the early puerperium.

What is the function or purpose of the Braxton Hicks contractions? Braxton Hicks himself suggested that they aid the circulation of blood through the uterine and placental sinuses and assist in adapting the position of the fetus to the form of the uterus.⁵ There also can be no question but that a muscular organ, if it is to grow and maintain its tone, must contract. An additional and extremely important function appears to be concerned with the changes that occur in the arrangement of the muscular elements of the uterus during the course of pregnancy. These changes, which are essential preparations for labor, include the division of the uterus into upper and lower segments, some degree of cervical effacement, and in some women (particularly multiparas) partial dilatation of the cervix.¹⁷⁻¹⁹

RESPONSE TO PITUITRIN

CASE 6.—M. S., white, 39 years of age, a multipara, entered the hospital at term with false labor pains which soon subsided. Fig. 5, *C* is a tracing taken during the course of an unsuccessful Watson induction and is presented to demonstrate the effects of pituitrin on the pregnant uterus. During the control period of ten minutes, there was little myometrial activity. Clonic contractions appeared soon after the subcutaneous injection of 1 I.U. of pituitrin and continued at fairly regular intervals for about fifty minutes when a second injection of 2 I.U. was given. This was followed almost immediately by a tetanic contraction of five minutes' duration. The clonic contractions then reappeared but did not persist. The patient was sent home and returned to the hospital two weeks later when the membranes ruptured. Labor began spontaneously and terminated thirty minutes later in the birth of an 8-pound infant.

According to Murphy there is a significant relation between the response to pituitrin administered during late pregnancy and the length of labor.²⁰ He also noted that the response to pituitrin occurred more often (a) in multigravidas than primigravidas, (b) during than before labor, (c) later in pregnancy than earlier, (d) after larger than smaller doses of pituitary extract, and (e) when the uterine wall was tense than when it was relaxed.²¹

UTERINE INERTIA AND THE EFFECT OF ANALGESIA

CASE 7.—H. F., white, 21 years of age, a primigravida, entered the hospital eleven days past the expected date of confinement with mild infrequent labor pains and ruptured membranes of twenty-four hours' duration. The pains soon increased in frequency and intensity. Analgesia in the form of morphine sulfate (gr. $\frac{1}{6}$) and scopolamine hydrobromide (gr. $\frac{1}{150}$) was administered by subcutaneous injection. The pains ceased shortly afterwards. Fig. 5, *D* is a tracing taken twelve hours after the analgesia was given. The cervix was now two fingers dilated. The tracing reveals the presence of small, frequent, arrhythmic contractions of short duration. Typical labor contractions are absent. The pains returned 4 hours later following a hot enema and continued at regular intervals for 10 hours when spontaneous delivery occurred.

The effect of analgesia administered during labor is often unpredictable. In some instances the contractions increase in frequency and intensity and precipitate delivery may occur. In other cases there is no effect on the contractions.

HYDATIDIFORM MOLE

CASE 8.—E. L., a 42-year-old white woman, was admitted to the hospital with a history of amenorrhea of eight months' duration. The uterus, however, was the size of a six months' gestation. Fetal heart sounds, movements, and parts were absent. One-tenth cubic centimeter of urine gave a strongly positive Friedman test. External hystero-graphy revealed the presence of both the large and small contractions occurring in the characteristically irregular pattern of pregnancy (Fig. 5, *E*). A hydatidiform mole was later removed by abdominal hysterotomy. It is interesting to note that Braxton Hicks had recognized the presence of contractions in this condition.⁵

CONCLUSIONS

Pregnancy, aside from the development of the fertilized ovum, is merely a continuation of the luteal phase of the menstrual cycle. The same hormones (estrogen and progesterone) are produced by the corpus luteum and the placenta, and the same irregular type of myometrial activity takes place. Apparently the arrhythmic contractions of pregnancy gradually bring about a division of the uterus into an upper and a lower segment and some degree of effacement and dilatation of the cervix. These preparatory steps in the expulsion of the fetus are rapidly completed by the rhythmic contractions of labor whose appearance is rather abrupt. Labor may be regarded as the terminal event of a process designed to expel the products of gestation that begins at the time the ovum is fertilized. Just what it is that usually prevents premature emptying of the uterus is still a question. When this is known we may understand the cause of the onset of labor.

Grateful acknowledgment is given to Dr. Harry Aranow, Director of Obstetrics of Morrisania City Hospital, for permission to conduct this study and to Professors Charles C. Lieb and Michael Mulinos of the Department of Pharmacology, College of Physicians and Surgeons, Columbia University who have generously provided the necessary equipment and many helpful suggestions. The posterior pituitary solution used in this study was supplied by E. R. Squibb & Sons through the courtesy of Dr. J. A. Morrell.

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The development of breast cancer in 1,206 women, whose breasts had been operated upon for benign noninfectious lesions of the breast, was studied and compared with the incidence of breast cancer in females of the general population in the same age groups.

While the data are insufficient with regard to adenoma and adenocystoma, they do indicate that adenoma is without significance as regards subsequent malignancy, and that adenocystoma is a precancerous lesion.

When age specific rates are used, the breast cancer attack rate for women with chronic mastitis and related lesions in the age group from 30 to 49 years is 11.7 times the rate for the Massachusetts female population; in the group over 50 years of age, 2.5 times as great; in the entire group, 4.5 times as great.

Chronic cystic mastitis and chronic mastitis predispose to the development of breast cancer. No means at present exist to determine those lesions which will develop cancer and which will not. The risk is not sufficiently great to warrant bilateral mastectomy in cases of chronic mastitis and chronic cystic mastitis.

Patients in whom these lesions are found on operation should subsequently be carefully watched and simple mastectomy done if nodules or cysts develop in residual breast tissue.

THE COMPARATIVE PHYSIOLOGY OF PLACENTAL TRANSFER

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THE questions concerned with placental permeability or placental transfer which have, until recently, been put to experimental test, are very largely concerned with the problem of whether a particular substance will pass through the placenta. These substances vary from metabolites^{1, 2} and hormones^{3, 4} of obvious and important interest to fetal physiology, to molecules supposedly of graded size used to estimate the limit of placental permeability.⁵ A few of these studies have been performed with the concept of comparative physiology in mind; the importance of this approach rests in the wide differences found in the histologic structure of the placenta in different species of animals. The conclusion to be drawn from such studies is that the placentas which morphologically appear less permeable are in fact less permeable when tested physiologically. Thus, for example, antibodies pass the human placenta, which is hemochorial, but not the syndesmochorial placenta of the cow.^{6, 7}

An important step was taken by Lell, Liber, and Snyder⁸ who proposed, by studying the rate of transfer of phenolsulfonphthalein from fetus to mother, to investigate possible changes which might take place in the rate of placental transmission at various parts of gestation in the rabbit. A similar step was later taken by Rodolfo⁹ in an effort to measure changes in permeability of the placenta to antibodies at different parts of pregnancy. Both sets of data lead to the conclusion that the rabbit placenta of late pregnancy is more permeable than that of early pregnancy.

Before the principles underlying placental transfer can be well understood, the following questions must be answered. Does the permeability of the placenta vary with the period of gestation? If the answer be positive, what are the underlying causes for the variation? Are there differences in permeability among the several morphologic types of placentas? Is the quantity of substance transferred across the placenta related to the rate at which the fetus is growing? Does the placenta act as an inert membrane or filter placed between the maternal and fetal circulations or does it modify the transmission of substances by contributing energy to the process and so acting as an organ of secretion? How is the failure of a substance to pass the placenta related to its physical and chemical characteristics? What effects do pathologic

processes have upon placental transmission and so upon the nutrition of the fetus?

Ideally, from an experimental standpoint, one should be in a position to study the problems with several or many test substances; and these substances should be as closely related as possible to those molecules which normally pass the placenta. The advent and development of stable and radioactive isotopes, together with reliable methods of exquisite sensitivity for their detection, has furnished a method which satisfies this criterion. The isotope may be used to identify or "mark" a molecule (e.g., heavy hydrogen of atomic weight 2 replaces its isotope, hydrogen of atomic weight 1, in heavy water) and the molecule subsequently traced by detecting the isotope. Or the isotope may be studied directly as an ion (e.g., Na^{24} which is radioactive and which is detected by an instrument used for measuring radioactivity).

The present paper brings together the results of several separate investigations on the comparative physiology of the placental transfer of radioactive sodium. This substance was chosen as the beginning tracer material, because it is easily prepared by the cyclotron or electrostatic-pressure generator, its behavior in the body is not complex, and it is one of the physiologically important chemical building stones of the organism. In all instances, it has been used in a concentration far below the toxic level.¹⁰

The details of the experimental procedure may be found in the original communications.¹¹⁻¹⁶ Suffice it here to say that the essential steps were, (a) intravenous injection of the radioactive sample into the mother, (b) removal of the fetus by abdominal hysterotomy at a known interval, about an hour, after the injection, (c) measurement of the placental weight and fetal weight, (d) measurement of the radioactivity present in the ashed remains of the fetus and in a sample of maternal blood plasma.

The data from the various observations on the guinea pig, rat, rabbit, cat, goat, and sow have yielded the following correlations: (1) correlation of rate of transfer across a unit weight of placenta with the period of gestation, (2) correlation of transfer rate across the placenta with respect to morphologic type of placenta, (3) correlation of change in transfer rate to fetus with variation of relative growth rate of fetus. These correlations will now be discussed separately; the details of the observations may be found in the original communications.¹¹⁻¹⁶

1. *Variation of the Rate of Transfer Across a Unit Weight of Placenta With the Period of Gestation.*—The transfer rate per unit weight of placenta is obtained for a particular period of gestation by calculating the amount of sodium transferred to the total fetus in a known period of time and dividing this quantity by the weight of the placenta.

The results of the observations on the six animals which have been studied are given in Fig. 1. To represent all of them on a common chart,

it has been necessary to plot, at fractional parts of the gestation period, the transfer rate per unit weight of placenta in terms of the maximum rate which is observed near term. This is obviously required because, among the several animals, there are wide differences both in length of gestation period and magnitude of placental rates.

The amount of sodium (Na) supplied to the fetus in a unit time can be obtained readily from the quantity of radioactive sodium (Na^{24}) found in the fetal ash and maternal plasma. The Na^{24} present in the maternal circulation is thoroughly mixed with all the Na of the maternal plasma. Any Na^{24} which passes from the mother to the fetus is accompanied by Na from the mother and in the same proportion as holds for the maternal plasma since the two isotopes, in this regard, behave equiva-

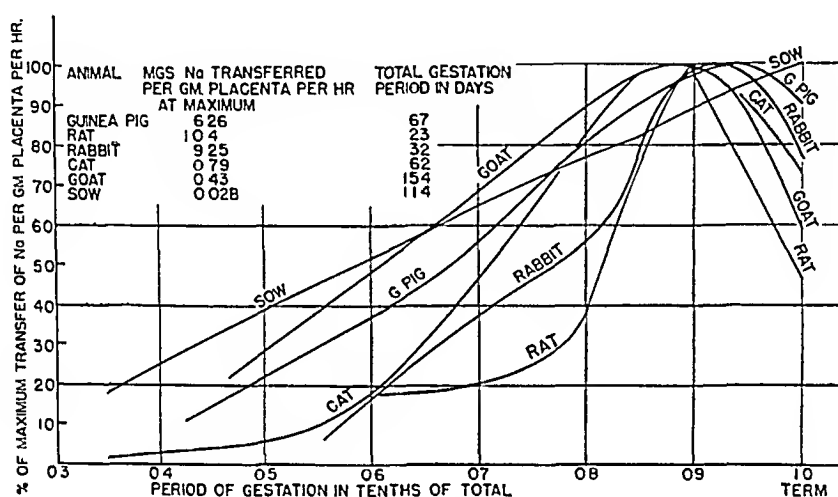


Fig. 1.—Variation of rate of transfer of sodium across unit weights of the indicated placentas with the period of gestation. As explained in the text, the actual quantity of sodium which is transferred across a gram of placenta can be calculated from the data of the figure for any day of gestation.

lently. If the concentrations of Na and Na^{24} in the maternal plasma be designated, respectively, by $\text{Na}_{\text{M.P.}}$ and $\text{Na}^{24}_{\text{M.P.}}$, and the total Na and total Na^{24} transported to the fetus per hour by $\text{Na}_{\text{T.F.}}$ and $\text{Na}^{24}_{\text{T.F.}}$, then:

$$\frac{\text{Na}_{\text{T.F.}}}{\text{Na}^{24}_{\text{T.F.}}} = \frac{\text{Na}_{\text{M.P.}}}{\text{Na}^{24}_{\text{M.P.}}}$$

Hence
$$\text{Na}_{\text{T.F.}} = \frac{\text{Na}_{\text{M.P.}}}{\text{Na}^{24}_{\text{M.P.}}} \times \text{Na}^{24}_{\text{T.F.}}$$

The concentration of Na in the maternal plasma has been assumed to be 3.3 mg. per c.c. in each instance. The actual amount of sodium passing across a unit weight of placenta on a particular day of gestation can be readily found with the values read from the graph together with values presented in the table of Fig. 1. For example, suppose one wishes to know the transfer rate per gram placenta in the case of the rabbit at the twenty-third day of gestation. The total gestation period in the rabbit is thirty-two days. The twenty-third day, consequently, is 0.72

of the total gestation period. The transfer rate at this time, as is evident from the graph, is 41 per cent of the observed maximum, and this maximum, as is to be seen in the table, has a value of 9.25 mg. of sodium per gram placenta per hour. Hence, each gram of the rabbit's placenta on the twenty-third day of pregnancy transfers 3.8 mg. Na per hour.

Fig. 1 shows that the six placentas all have the common characteristics of an increase in transfer rate as pregnancy proceeds. So far as the data are concerned, this change is most pronounced in the cat. A unit weight of the cat's placenta shows an increase in transfer rate of about 67 times from the middle of the third tenth of gestation to the maximum observed just before term. The observed change in the transfer rate is least spectacular in the goat, where it increases about five times during approximately the last half of gestation.

With the exception of the sow, all the placentas also have in common a peak or maximum transfer rate per unit weight shortly before term with a sharp drop in transfer rate as term is approached.

These findings immediately recall one of the questions asked in the introduction to this paper: What are the underlying causes for the observed increase in transfer rate per gram of placenta? A satisfactory answer to this question must involve quantitative knowledge of possible changes in such factors as size of placental capillary beds, rate of placental capillary blood flow, surface area across which exchange occurs, etc. All of these factors are unsatisfactorily understood. An important contribution has been made by numerous studies of Barcroft and his collaborators.¹⁷⁻¹⁹

Of clearer meaning at the moment are those morphologic changes found to occur as the placenta ages. A correlation can be made between changes in the placental structure and changes in the rate of transfer at different periods of gestation, but these are necessarily crude because of lack of quantitative measurements of tissue and cell relations. However, the general picture is clear and consistent. In the sow, there is a progressive diminution in the heights of chorionic and uterine epithelia.¹⁶ In the goat, chorionic villi are covered with an inner cellular and an outer syncytial layer; in the later stages of pregnancy, the inner cellular layer thins and the syncytial layer becomes discontinuous. The cat, like the goat, has an inner cellular and an outer syncytial layer, and in this case aging of the placenta is accompanied by reduction in height and in places disappearance of the cellular layer. The rat, guinea pig, and rabbit, in the earlier part of the gestation period, have chorionic villi covered with a single layer. In later pregnancy, this layer thins and disappears to such a large extent that Mossman²⁰ has suggested the term "hemo-endothelial" for the placenta at this period. The fall in transfer rate near term is in all likelihood due to senile changes in the placenta, such as thrombosis of the maternal vessels with infarction, etc.

Fig. 2 presents the changes in rate of transfer of sodium across a unit weight of the rabbit's placenta as gestation proceeds. The figure also gives in schematic form those changes in the chorionic plasmodium or syncytium which have been described by Mossman²⁰ at various periods of gestation. The syncytium is complete at the eighteenth day, at the twenty-fifth day it is discontinuous, and it has practically disappeared at the thirtieth day. The transfer rate of Na across the placenta increases as these changes occur. The figure consequently presents the sort of correlation which can be made between known morphologic changes and the observed changes in function.

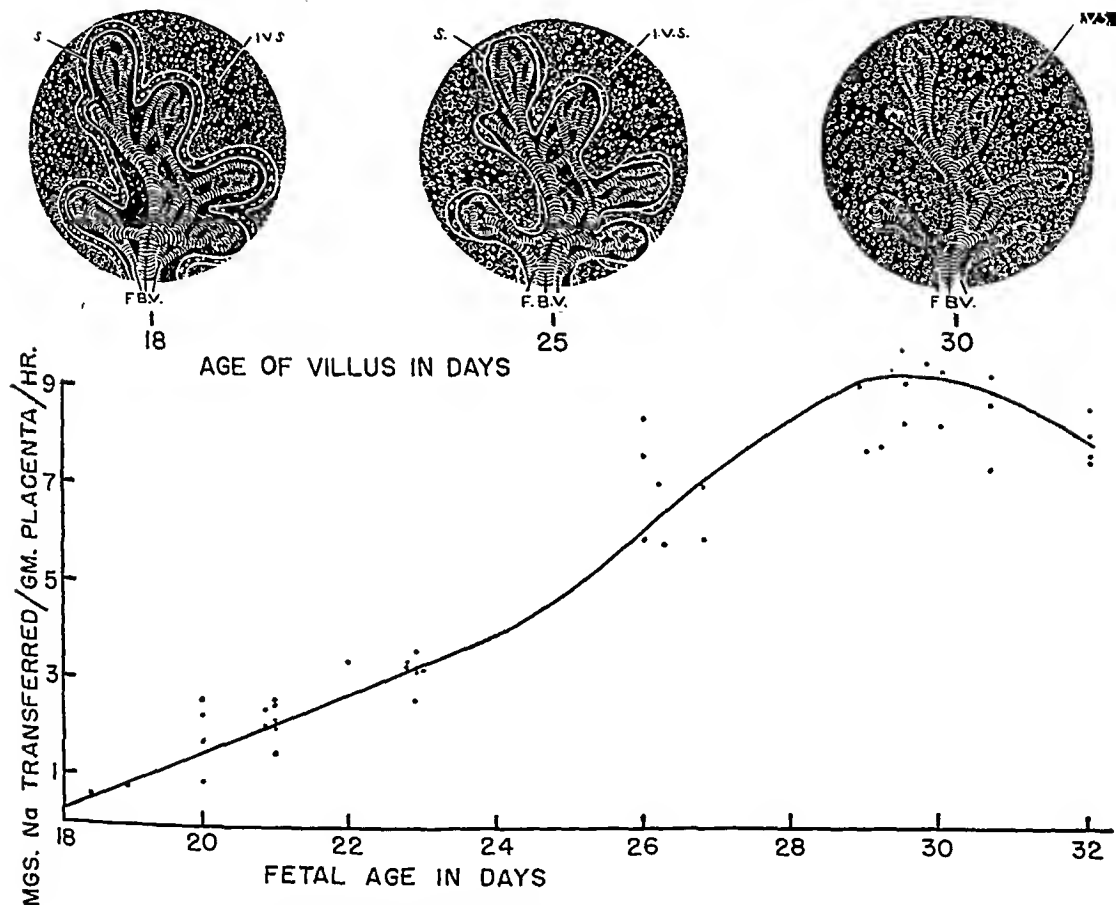


Fig. 2.—Changes in rate of transfer of sodium across a unit weight of the rabbit's placenta at different periods of gestation. The diagrams of the villi indicate the type of morphologic change which can be correlated with the functional change. F.B.V., Fetal blood vessels; I.V.S., intervillous space; S., syncytium.

If this correlation be valid, an inspection of Fig. 1 indicates those intervals during which the maximum morphologic and physiologic changes in the placenta would be expected to take place. For example, in the case of the rat we would anticipate that more striking changes would occur between the eighteenth and twenty-second day than during those preceding. This is the period during which the transfer rate increases most rapidly.

2. *Correlation of Transfer Rate and Morphologic Type of Placenta.*—Grosser²¹ has classified all placentas into four groups. This grouping depends upon the number of tissue layers separating the maternal and fetal circulations, as is evident from Table I, which has been taken from

TABLE I. CELLULAR LAYERS BETWEEN MATERNAL AND FETAL CIRCULATION.
GROSSER'S CLASSIFICATION OF PLACENTAS

TYPE OF PLACENTA	MATERNAL			FETAL			EXAMPLES
	ENDOTHELIUM	CONNECTIVE TISSUE	EPITHELIUM	EPITHELIUM	CONNECTIVE TISSUE	ENDOTHELIUM	
Epithelio-chorial	+	+	+	+	+	+	Sow
Syndesmo-chorial	+	+	—	+	+	+	Goat, sheep, cow
Endothelio-chorial	+	—	—	+	+	+	Cat
Hemo-chorial	—	—	—	+	+	+	Guinea pig, rat, rabbit, man

Grosser. One of our purposes has been to study the variations in transfer rate which occur among these four types of placentas. It is apparent that a measure of the variation among placentas of the same group must be obtained in order to appraise properly differences in the behavior of placentas belonging to different morphologic groups. For this reason we have chosen to study one member of each of three groups and three members of the fourth group. The sow has been taken because it belongs to the epitheliochorial group; the goat, because it is syndesmochorial; the cat, because it is endotheliochorial; and the rat, rabbit, and guinea pig have been chosen as representatives of the hemochorial group. We have compared the transfer rates across these different placentas at corresponding parts of the total gestation period.

Fig. 3 presents schematically the type of tissue layers placed between maternal and fetal circulations in Grosser's four groups. Above the diagrams of the placentas, there is indicated graphically the amount of sodium transferred per gram of placenta per hour midway between the eighth and ninth tenths of gestation. Two important conclusions are evident from the data of the figure. The first is that there is little variation in transfer rate among the members of a single group. The maximum variation is between the rat and guinea pig, the former having a transfer rate approximately 40 per cent greater than the latter. This close correspondence holds as well for earlier and later stages of pregnancy.^{13, 15} The second conclusion is that the greater the number of tissue layers placed between maternal and fetal circulations, the lower the unit transfer rate. Thus, the unit transfer rate of the rat's placenta with three tissue layers is 320 times that of the sow with six layers. It is also to be noted that the difference between the goat, a representative

of the syndesmochorial group, and the cat, of the endotheliochorial group, is relatively slight.

3. *Correlation Between Relative Growth Rate of Fetus and Rate of Transfer of Sodium to Fetus.*—Does the fetus receive a constant supply of sodium from the mother during the gestation period and incorporate with growth the amount which is needed while the remainder is returned to the maternal circulation? Or, does the supply of sodium vary during the gestation period according to the rate of fetal growth? The answer to these questions can be obtained by comparing the supply of sodium to a gram of fetus per unit time with the rate at which that gram of fetus reproduces itself. The first of these two quantities is found by

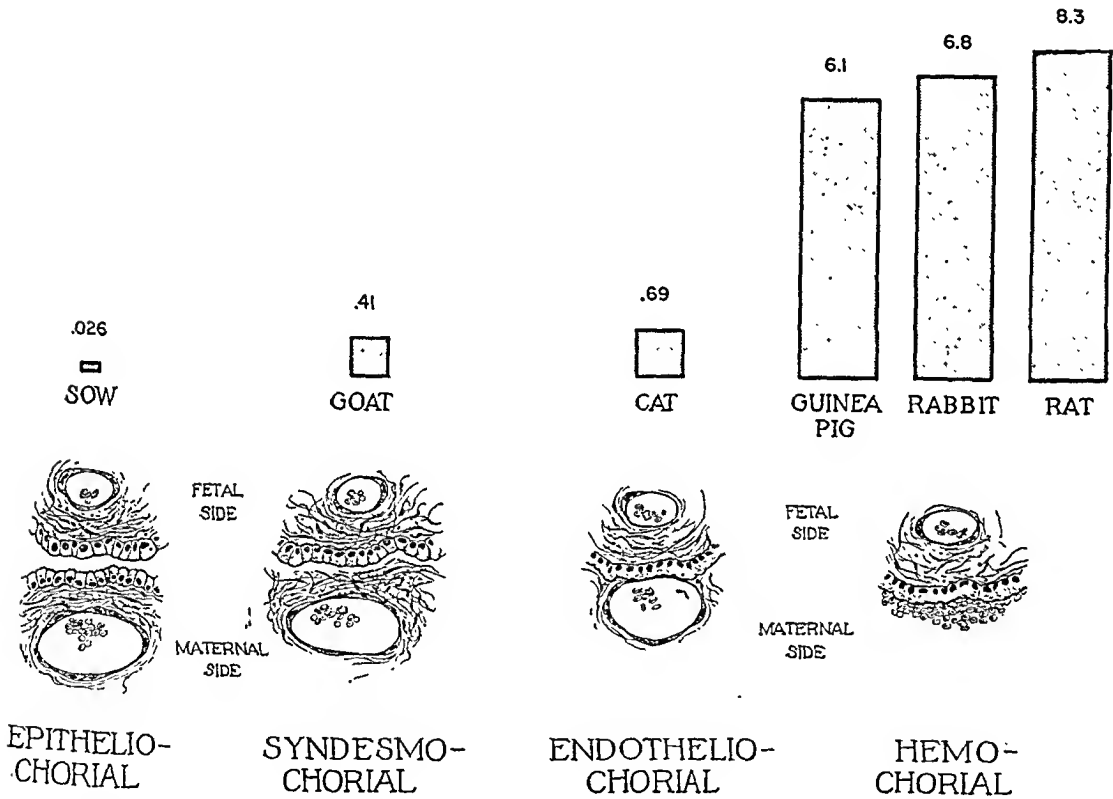


Fig. 3.—Variation of transfer rate per unit weight of placenta with the morphologic type of placenta. The numerical values give the mg. of Na transferred across a unit weight of placenta per hour as observed in each instance at the middle of the ninth tenth of pregnancy. The relative magnitudes of the transfer rates are indicated by the relative areas of the dotted rectangles. The diagrams indicate the number and kind of tissue layers interposed between maternal and fetal circulations in each of Grosser's four groups.

simply dividing the total sodium transferred to the fetus per hour by the fetal weight. The second quantity is the relative growth rate of the fetus and is obtained in a manner previously given¹¹ from the data relating fetal weight to gestation age. If the placenta is nicely adapted to the needs of the fetus, one would expect a large amount of sodium to be transferred per gram fetus when the relative growth rate is high, since sodium is an integral part of each unit mass of tissue, and a lower transfer rate per gram fetus when the relative growth rate is low.

Fig. 4 gives the relative growth rate and the transfer rate of Na per gram fetus at progressive fetal weights for the cat. It is evident that the two curves are similar; when the fetus is small and a unit weight of its tissue is reproducing itself rapidly, the transfer rate of Na to a unit weight of fetus is high, and as the fetus grows older and its relative growth rate drops, the supply of sodium per unit weight of fetus is commensurately low. This finding in the cat is typical of that observed in the other animals which have been studied.¹¹⁻¹⁶

These results can be expressed in another way. As has been said, the curves of relative growth rate and rate of supply of sodium are similar. If this be strictly true, it follows that the rate of supply of sodium to a unit weight of fetus times a constant quantity should be equal to the relative growth rate at any fetal weight or fetal age, or $K = \text{relative growth rate} \div \text{transfer Na per gram fetus per hour}$. The precision with

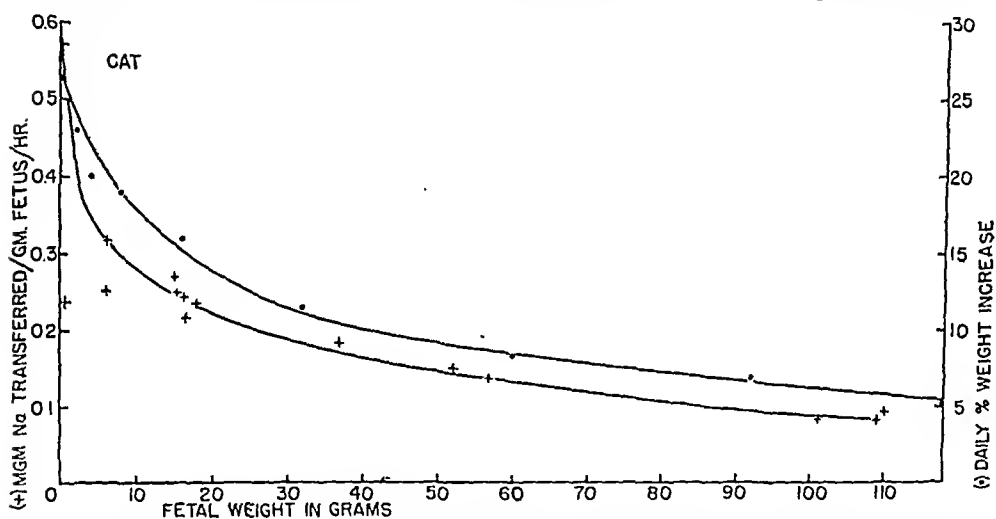


Fig. 4.—Comparison of curve of daily percentage weight increase and curve of transfer rate of sodium per gram fetus for the cat during the gestation period.

which this concept fits the observations will be evident from the variation in K at various parts of gestation. The value for K for the several animals and at different periods of pregnancy is given in Table II. It is apparent that the variation in K for a particular animal is remarkably small.

These findings suggest the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus.

We have been further interested to inquire whether wide differences in the relative growth rates of the fetuses of different animals can be correlated with differences in the rate at which sodium is supplied to a unit weight of fetus. Thus, it can be seen in Table II in the middle of the seventh tenth of gestation that the rabbit is reproducing its weight at the rate of 25 per cent daily, whereas the goat is reproducing its